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According to  
**Annals of  
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 October, 1930

"A VERY COMMON-SENSE TREATMENT of the subject of functional or so-called 'nervous indigestion.' More than half of the patients who go to a physician for advice in regard to chronic indigestion have symptoms apparently largely 'functional' in nature. No organic lesions can be demonstrated in them, and no definite anatomic diagnosis can be made. Because of the difficulty in making a diagnosis, these patients are for the greater part neglected. . . .

. . . . Teachers are interested in the demonstrable lesion, and not in cases in which lesions cannot be found and in which a definite diagnosis cannot be made. Consequently the student is not prepared for the problems involved in the treatment of the so-called 'nervous' patient. . .

. . . . That this field is a neglected one in the medical schools is evident to anyone who attends the lectures or clinics, or makes ward rounds. As a consequence it is a far cry from the medical practice of our teaching clinics to the private practice of a down-town office. In the latter place the young practitioner will learn that in the actual practice of medicine there are many things more important than the giving of drugs or the exploratory operation. . . .

. . . . The material is presented in a semi-popular style, suitable for reading by the laity, for whom it is apparently intended as much as for the practitioner. And it is worth their perusal. In Chapter Two on Types of Indigestion many grains of pure gold are to be found. This chapter should be read by all those who have 'indigestion,' and who have an interest in 'diets' or 'dieting.' How certain Sanitarium authorities must gnash their teeth when they read it! The reviewer, as a pathologist, finds himself strangely in agreement with a gastroenterologist for the first time. **THIS BOOK IS IMPORTANT BECAUSE OF THE TRUTHS IT TELLS.** The style is vivacious. The chapters are interleaved with pages of fact and interesting quotations from a great variety of sources. They add a literary flavor to the exposition of sound sense contained in this book."

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BY

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## Diagnostic and Physiologic Studies in Certain Forms of Scleroderma\*

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**S**CLERODERMA is the term that has been applied to a syndrome characterized by induration, pigmentation, and sclerosis of the skin, associated with loss of weight, asthenia, arthritis, atrophy of muscles and other symptoms, depending on the degree and extent of the hidebinding. Cases of the disease may be divided into two groups: the diffuse or generalized form, and the localized form known as morphea or circumscribed scleroderma. The group known as morphea will be eliminated from this report.

The onset of the diffuse form of scleroderma varies. It may be ushered in with symptoms of arthralgia, malaise, loss of weight, and asthenia; or it may develop acutely following systemic infection, frequently interpreted as influenza; other cases have been observed to follow, and seem definitely related to, acute arsenism. Among the most frequently observed cases are those in which the scleroderma starts insidiously and pursues a slow, pro-

gressive course, and in which there is no discernible etiology. The cases, with which this paper is chiefly concerned, are composed of the patients in whom evidence of Raynaud's disease is associated with the scleroderma. (Table 1).

The dermatologic features of the disease are the same, irrespective of the mode of onset; hence it is impossible to classify the disease from its clinical appearance. However, the distribution may give a clue as to the mode of onset, that is often confirmed by the history. The etiology of scleroderma is unknown, so that our classification of the disease according to the mode of onset was adopted as a means of grouping the cases from the standpoint of therapeutics rather than from that of etiology. In the literature may be found a variety of explanations and hypotheses with regard to the etiology of scleroderma, and for detailed material the reader is referred to the article by Boardman who recently thoroughly reviewed the literature. The present conception of the etiology of scleroderma may be summarized briefly in the statement that a variety of noxae have been

\*Read before the American College of Physicians, Minneapolis, Minnesota, February 10 to 14, 1930.

TABLE I.  
GROUP I: PRIMARY SCLERODERMA; VASOMOTOR DISTURBANCE APPEARED AFTER THE SCLERODERMA WAS WELL DEVELOPED.

Case	Age, years, and sex	Duration of disease, months	Duration of vasomotor disturbances	Duration of sclerodermal changes	Extent of sclerodermal changes	Disability and progression	Classification of cases
1	37 M	15	One month, slight color changes.	Fifteen months, swelling in hands; one year, in duration.	Face, neck, hands and arms.	Rapid progression for six months; 75 per cent disability.	Primary scleroderma; short duration; severe form.
2	41 M	18	One year, cyanosis of hands with cold.	Eighteen months, progressive stiffening of skin of hands.	Fairly generalized; most marked in hands, arms, face.	Progressive weakness; rapid increase in induration of skin; 75 per cent disability.	Primary scleroderma; short duration; severe form.
3	30 M	24	Eighteen months, cyanosis of hands with cold.	Twenty-four months, swelling of hands, then hardening of skin.	Hands, arms, face and neck, partial fixation of joint.	Marked weakness; muscular atrophy; pigmentation, graded 3.00 per cent disability.	Primary scleroderma; short, rapid course.

recognized as factors in the production of the disease, and that one or several of these noxae may be involved in a given case. Among the outstanding causes may be cited infections, arsenism, trauma, vasomotor diseases in the extremities, and dysfunction of the glands of internal secretion, particularly of the thyroid gland.

Watson, in 1754, reported the first case, as quoted in detail by Willan in 1808. In 1895 Lewin and Heller reviewed a series of 508 cases, and three years later Osler reported a series of eight cases, in one of which the history was that of a syndrome resembling Raynaud's disease which preceded the onset of the scleroderma and sclerodactylia. The Raynaud-scleroderma syndrome has been recognized repeatedly since, and has been the basis for the conception that scleroderma is attributable to vasomotor neurosis, angioneurosis, or angiotrophoneurosis. Cassirer recognized the relationship to vasomotor disease, and divided scleroderma into three types: the Raynaud type, the vasomotor type without gangrene, and the typical form, in which, late in the disease, Raynaud symptoms with gangrene develop. We have modified this classification slightly and group the cases of the vasospastic type of scleroderma with sclerodactylia into those in which the sclerodermal process has been the primary disturbance (table 1), and vasomotor disturbances, which are often absent, appear, if at all, relatively late; those cases (table 2), in which the vasomotor disturbances appear simultaneously with the onset of the sclerodactylia, and those in which the vasospastic disturbance precedes the appearance of the scleroderma or

the sclerodactylia by months or years (table 3).

In a clinical study of 103 cases of scleroderma, O'Leary and Nomland found that in 33 per cent of the cases of generalized scleroderma there was a definite history of vasomotor phenomena in the extremities preceding the onset of the sclerodactylia. The severity of the vasomotor symptoms in this group was variable, ranging from moderate cyanosis on exposure to cold, to the more severe cases, in which were all the evidences of typical Raynaud's disease, with the white, blue, and red stages, and the accompanying pain. In cases of the vasomotor type, the scleroderma manifested itself first in the hands (sclerodactylia) and gradually extended up to the arm; the face and upper part of the thorax, and sometimes the feet, were involved simultaneously. It is not to be inferred from this that sclerodactylia is solely a manifestation of the vasomotor type of the disease, because O'Leary and Nomland noted sclerodactylia in 89 per cent of the cases with the generalized type of the disease. The five cases (11 per cent) in which there was no involvement of the hands, did not present evidence of vasomotor disease of the extremities.

The vasomotor type of this disease may readily be distinguished from the other varieties, not only from the history of the vasospastic disease, but also from the characteristic distribution, in which the hands, forearms, face, upper part of the thorax (fig. 1) and feet are primarily involved. This distribution is to be contrasted with other types of generalized scleroderma in which the trunk and face may show the

TABLE 2.  
TYPE 2: SIMULTANEOUS DEVELOPMENT OF SCLERODERMA AND VASOMOTOR DISTURBANCES\*

Case	Age, years, and sex	Duration of disease, months	Duration of vasomotor disturbances	Duration of sclerodermal changes	Extent of sclerodermal changes	Disability and progression
4	50 F	18	Eighteen months, pallor, and cyanosis of hands with cold.	Seven months, stiffening of skin of hands, face and neck, with intermittent swelling of feet.	Generalized, except back of thorax; fixation 50 per cent in fingers; dry ulcers of knuckles.	75 per cent in upper extremities.
5	55 F	24	Twenty-four months, cold hands and cyanosis with swelling of fingers.	Twenty-four months, swelling in hands, six months rapid progression of scleroderma in face and arms.	Upper extremities, face, neck and thorax.	Mild weakness; disability 30 per cent in hands.
6	19 F	24	Twenty-four months, pallor, numbness and swelling of fingers.	Twenty-four months, swelling in hands; twelve months hardening of skin in hands; cyanosis with cold.	Hands, arms, face and thorax; mild in feet.	Mild weakness; about 30 per cent disability in hands.
7	34 M	42	Forty-two months, pallor, cyanosis, numbness, stiffness of skin in hands.	Forty-two months, numbness and stiffness in hands; six months rapid progression of induration of skin.	Hands, arms, face, neck and thorax; feet and lower legs, muscular atrophy.	70 per cent disability in hands; painful joints and muscles.

\*All of these cases were classified as of the rapidly progressive form, with vasomotor symptoms appearing with the onset of scleroderma.



TABLE 3.  
GROUP 3. VASOMOTOR DISTURBANCES PRECEDING DEVELOPMENT OF SCLERODERMA

Case	Age, years, and sex	Duration of disease, years	Duration of vasomotor disturbances	Duration of sclerodermal changes	Extent of sclerodermal changes	Disability and progression	Classification of cases
8	24 M	5	Five years, blanching and cyanosis in hands with cold; recurring ulcers.	Six months, stiffness in skin of hands.	Hands, and feet, in feet.	50 per cent in hands.	Localized vasomotor form of scleroderma in acral areas.
9	32 F	5	Five years, attacks of pallor and cyanosis in hands with cold and nervousness; one year, same in feet.	Three years, stiffness in hands; ulcers one year in feet.	Hands, arms, face, neck and feet.	50 per cent in feet; 80 per cent in hands; mild weakness.	Chronic vasomotor form.
10	35 F	5	Five years, pallor and cyanosis, and pain in hands with cold.	Three years, ulcers and induration of skin of hands, painful.	Hands and face.	75 per cent in hands.	Chronic vasomotor form.
11	31 M	8	Eight years, changes of color in hands and feet.	Seven years, mild stiffness of fingers and face.	Hands, with ulcers; slight in face.	75 per cent in hands; mild weakness.	Chronic vasomotor form.
12	35 F	11	Eleven years, blanching and cyanosis in fingers with cold.	Ten years, swelling, ulcers of fingers; gradual progressive scleroderma.	Hands, arms, thorax and face (?).	60 per cent in hands.	Probably a vasomotor form; slowly progressive scleroderma.

TABLE 3 (Continued)

TYPE 3. VASOMOTOR DISTURBANCES PRECEDING DEVELOPMENT OF SCLERODERMA

Case	Age, years, and sex	Duration of disease, years	Duration of vasomotor disturbances	Changes of scleroderma	Duration of scleroderma changes	Extent of scleroderma changes	Disability and progression	Classification of cases
13	37 F	13	Thirteen years, pallor and cyanosis in fingers; six years, same in feet.	Three years, dry ulcers of hands.	Hands and face (?) ; 75 per cent in hands, feet cyanotic.	Chronic vasomotor form.		
14	44 F	15	Fifteen years, changes of color in hands with cold.	Ten years, ulcers of finger, pain graded 3.	Generalized on hands, face, neck and thorax, feet in stage of swelling.	Chronic vasomotor form.		
15	57 F	17	Seventeen years, changes of color in hands; five years, same in feet.	Ten years, stiffness of hands; flexion deformities.	Generalized; least in feet.	Chronic vasomotor form.		
16	25 F	22	Twenty-two years, cyanosis and pallor in hands, feet, and skin of body.	Nineteen years previously scleroderma changes appeared; continued with vasomotor disturbance.	Generalized; worse in hands and arms.	Chronic vasomotor form; regressive on body; loss of fingers from ulcers.		

greater degree of involvement, with the sclerodactylia absent or appearing as a late manifestation.

#### MATERIAL

This report concerns clinical and physiologic studies, and evaluation of surgical treatment, in sixteen cases of scleroderma in which vasospastic disease of the extremities was present. When the time of development of the vasomotor factor in relation to the appearance of the scleroderma was considered, three groups were recognized: (1) nine cases in which the vasomotor condition was primary; (2) four cases in which the sclerodactylia and the vasospasm appeared simultaneously, and (3) three cases in which the vasomotor disturbance developed after the appearance of the sclerodactylia. In all cases the skin of the hands was affected chiefly, but that of the arms, face, and thorax, and of the lower extremities, was involved in some degree. There were six men and nine women, with ages ranging from nineteen to fifty-seven years. The duration of the disease varied from one to twenty-two years. Several of these patients, when first seen, had the characteristic symptoms and signs of Raynaud's disease, without induration of the skin, but at subsequent observations the scleroderma was found to be well developed. In all of these cases, the scleroderma had progressed far enough to have produced atrophy of the appendages of the skin (figs. 2, 3, 4, and 5) with trophic ulcers of the fingers and regions of the knuckles, or of the extensor surfaces of the elbows. In case 9, the disease was present in a fairly early stage in the feet, probably representing

the first stage or the stage of swelling, whereas in the hands the process was well advanced. Pigmentation was present in some degree in every case, and in one case to a degree to be confused with Addison's disease (fig. 6). In Case 16, a period of regression of the scleroderma in the skin of the face, arms, and thorax had taken place, and the sole residue was the vasospastic disturbance of the fingers, melting ulcers of the finger tips, gangrene, and repeated symmetric amputation of the fingers.

#### HISTOLOGIC PATHOLOGY

The study of the pathologic changes in the skin in scleroderma has not thrown light on the etiology of the disease. Conversely, inadequate knowledge of the etiology makes it difficult to interpret the pathologic changes observed, not only those in the skin but also those found in the viscera at necropsy.

Ormsby has summarized the cutaneous pathologic changes in a well established case as being characterized by hypertrophy of the collagen, comparative absence of blood vessels, large numbers of dilated lymph spaces, hyperpigmentation both in the rete and the corium, and comparative absence of the glands of the skin. A variety of opinions has been recorded in regard to the relationship of these various pathologic processes; however, it seems agreed that the hypertrophy of the collagen results in phenomena due to pressure that interferes with the blood supply. The effects of pressure, and the local anemia, lead to atrophy of the appendages of the skin.

The reported observations at necropsy in cases of scleroderma are not

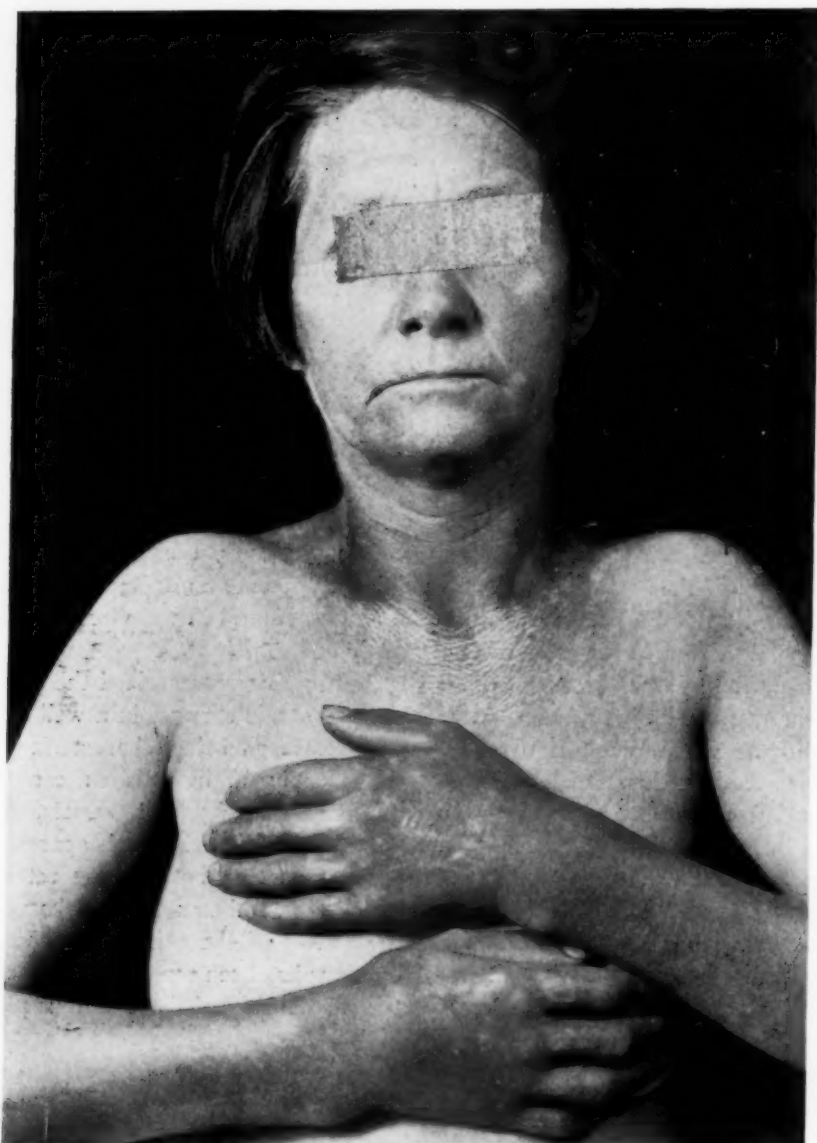


FIG. 1. The distribution of the cutaneous changes in an early case of the vasomotor type of scleroderma.





FIG. 2. Mild form of sclerodactylia.



FIG. 3. Sclerodactylia of more severe form than that shown in Figure 2.



FIG. 4. Severe form of sclerodactylia, with destruction of terminal phalanges.

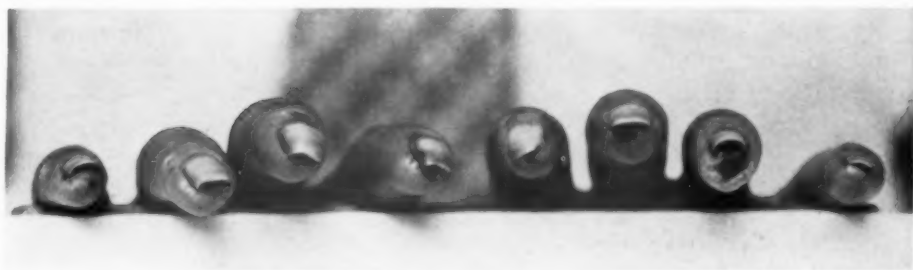


FIG. 5. Trophic ulcers in the vasomotor type of sclerodactylia.

numerous, but the six reports of cases made by Matsui are detailed. He stated that not only was there proliferation of the collagen in the skin and changes in the small, cutaneous arteries, but that similar changes were noted in certain of the viscera. These degenerative changes were in the lungs, kidneys, and endocrine glands. He studied the glands of internal secretion in detail and felt that, as a result of the changes noted, the etiology of scleroderma was attributable to endocrine dysfunction. We have studied sections of skin in advanced cases of the diffuse type, as well as from patients with the vasomotor type, and the changes are considerably similar; they differ, however, in the fact that in the latter type there is considerably more cellular infiltration, both within and around the small vessels of the skin. A detailed consideration of the significance of the cellular reaction is not possible, but this reaction is so common and pronounced that it suggests the possibility that the vascular changes are forerunners of some of the other pathologic features. It also seems justifiable to attribute the changes in the thyroid gland, in which sclerosis has been noted at necropsy, as the result of the systemic involvement, rather

than the cause of it. Particularly significant is the cellular infiltrate around and in the smaller blood vessels in the acute edematous phase of the disease, before the collagen deposits are well organized.

#### PHYSIOLOGIC PATHOLOGY

*Surface Capillaries:* Microscopic studies of the capillaries in the nailfold had been made previous to the time of this study by Brown and O'Leary. Similar studies have been made in all of these sixteen cases, and the significant changes were found to be sharp diminution in the number of open capillaries for each unit area of skin, and reduction to approximately a half or a third of the normal number. The capillaries, in this condition, are large, distorted, and irregular (figs. 7 and 8), and frequently one capillary of this type may be the only one seen in the field. The outlines of the capillaries are frayed, irregular, indistinct and appear as irregular masses of blood. The flow of blood through the loops is markedly disturbed. With slight lowering of the environmental temperature, the flow becomes slowed or stationary. The blood becomes deeply cyanotic in color, and with higher environmental or bod-



FIG. 6. Pigmentation of the hand severe enough to resemble Addison's disease, in the vasomotor type of scleroderma.



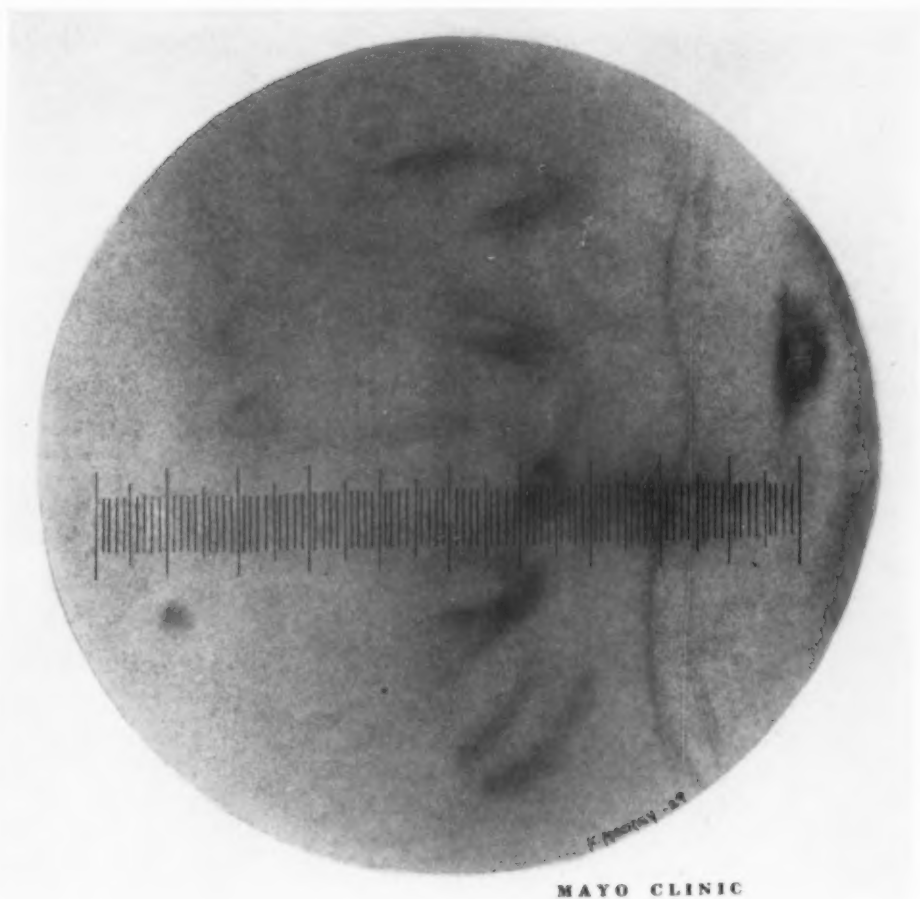


Fig. 7. (Case 5). Capillaries of the nailfold before operation.

ily temperature there is acceleration of the rate of flow, with transition to a reddish color. Marked impairment in the transparency of the skin is usual, which makes it extremely difficult to define the outlines of the loops. This is due probably to three factors: (1) the increased density in the skin, (2) perhaps the interference with the flow of lymph and accumulation of fluid, and (3) the pigmentation.

The most striking impression gained from examination of the capillaries is

the great reduction in the amount of circulating capillary blood in the skin. These changes explain the reduced temperature and the pale color of the skin. The marked susceptibility to slowing of the capillary flow with slightly reduced temperature, and the changes in color, reflect the exaggerated tonus of the arterioles. The excessive sweating of the hands of many patients also indicates excessive stimulation of the sympathetic apparatus. The changes in the surface capillaries

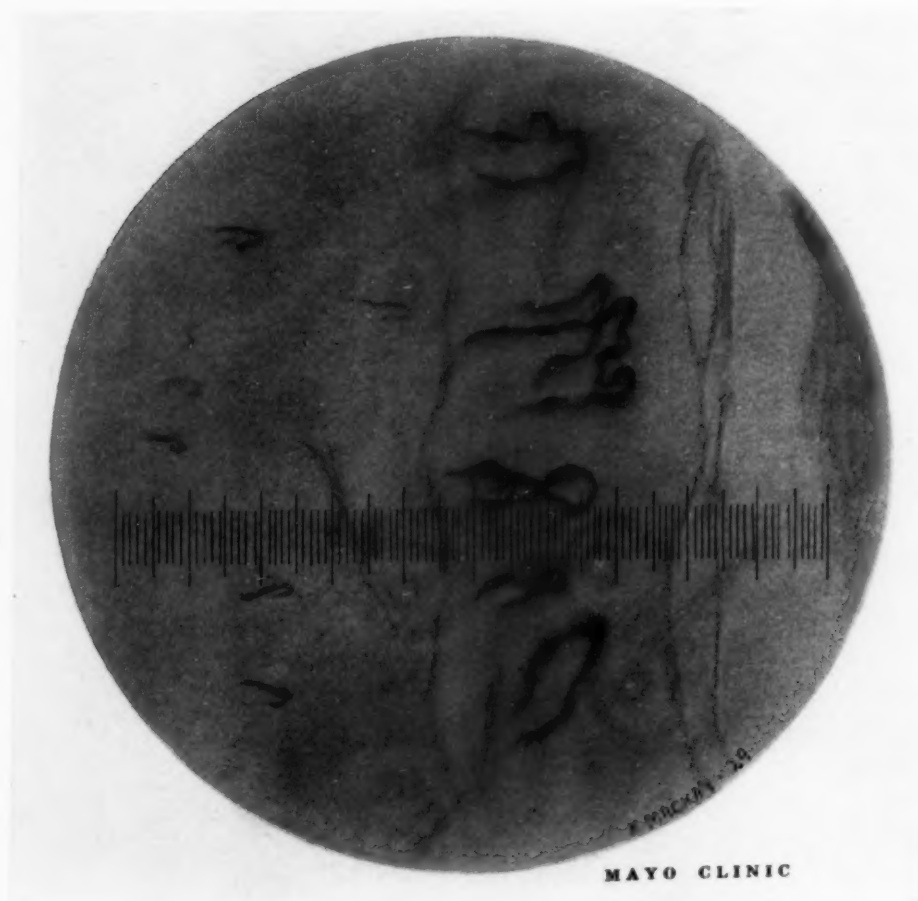


FIG. 8. (Case 5). Capillaries of nailfold after operation.

emphasize the fact that the major factor in a well advanced case is the lack of blood in the skin. This lack of blood is due to two factors: the increase in the collagen, which results in obliteration by pressure of the arterioles and capillaries, and an excessive degree of vasospasm in the arterioles. The determination of the magnitude of the vasomotor element will be considered later.

*Surface Temperature:* Determinations of surface temperature have been

carried out in the hospital under fairly constant conditions of environmental temperature. The skin of the hands or feet of a patient with sclerodactylia is usually cold and clammy, has a cadaveric appearance and the temperature of the hands and feet is lower than that of the surrounding air. In a normal subject, the average surface temperature of the fingers, as determined with the thermocouple, in a room in which the temperature is maintained at a range of  $24^{\circ}$  to  $26^{\circ}$  C., ranges between

32° and 35° C. In these cases, it varied from 19.6° to 29.8° C., averaging about 25.3° C. (fig. 9). In the earlier vasomotor forms of scleroderma, the temperature of the skin of the hands and feet may vary within a wide range. At times, the hands and feet are excessively cold; again, warm or even hot. This is further evidence of excessive hypertonus of the arterioles.

*Rates of Elimination of Heat:* In the hands and feet the rates of elimination of heat have been studied with the Stewart and Kegerreis calorimeter. This method, as explained by Sheard and by Brown<sup>4</sup>, determines, over a fixed period of time, the amount of heat eliminated from the limb and taken up by a given volume of water in which the limb is immersed. The loss of heat is expressed as small calories of heat eliminated from the entire hand for each minute of time. The rate of elimination of heat for the normal

hand averages about 100 small calories for each minute. This method of study is probably the best procedure for determining, in an indirect way, the volume flow of blood through the extremities, and constitutes an extremely valuable method for the comparative studies to determine the effects of treatment on volume flow of blood.

The mean value for nine cases of scleroderma was 34 small calories of heat eliminated for each minute (fig. 10). All had rates of loss of heat considerably less than normal. There was no significant difference in the values for the different forms of scleroderma included in this study.

*Vasomotor Indexes:* A method for determining quantitatively the amount of vasospasm in the extremity has been devised by Brown<sup>3</sup>. This method determines the so-called vasomotor index, which indicates the increase in surface temperature of the foot or hand for

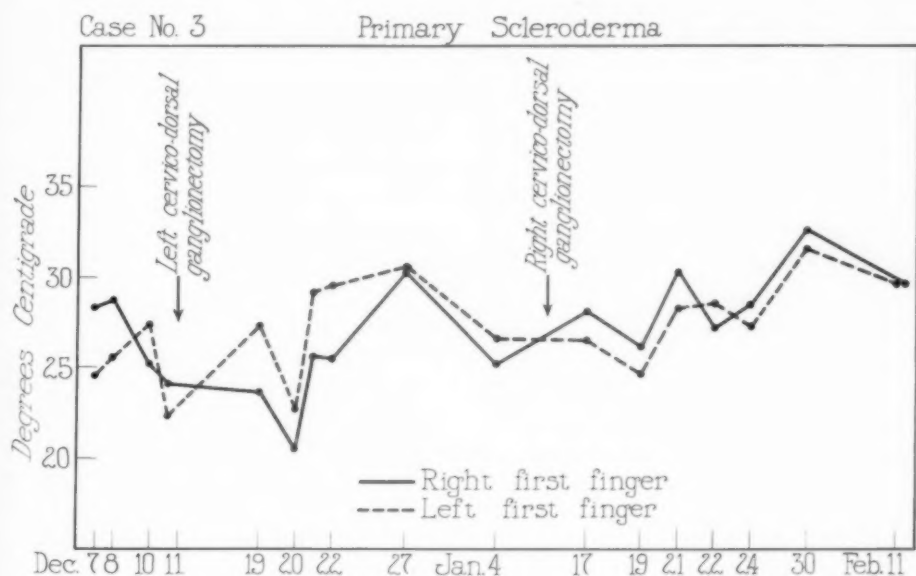


FIG. 9. (Case 3). Studies of surface temperature, before and after operation.

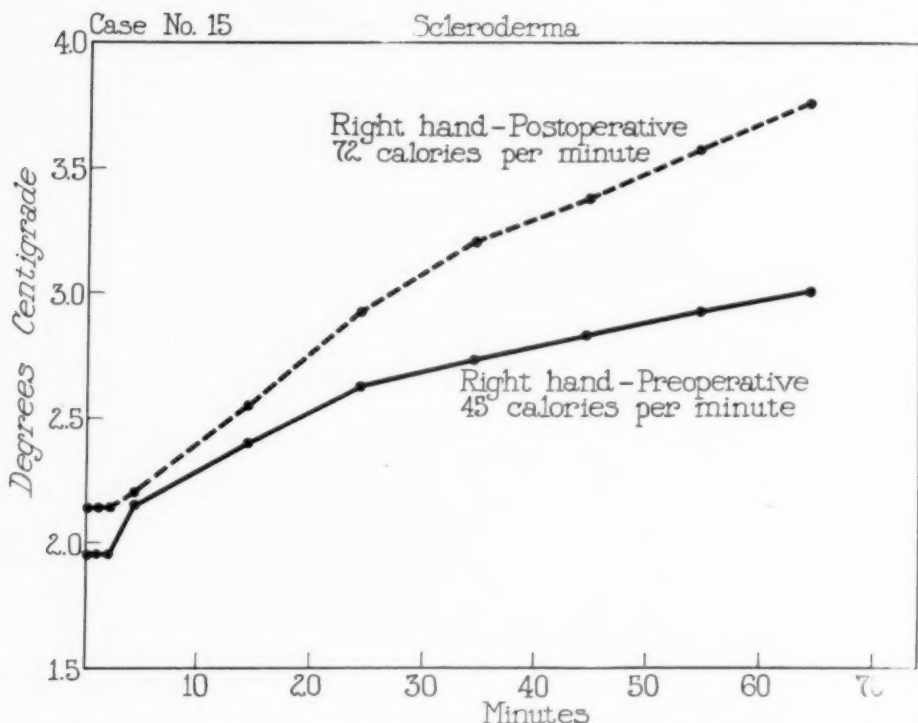


FIG. 10. (Case 15). Curve of elimination of heat before and after operation.

each degree of temperature of the body. In vasomotor disturbances of the spastic type, for example in Raynaud's disease, high indexes are obtained; frequently the value is 10 or more. In normal subjects, with warm hands or feet, low indexes are obtained. With occlusive disease of the arteries, such as thrombo-angiitis obliterans, wide variations are obtained, varying from less than 1 to 8. This is evidence that in some cases, with occlusive disease of the arteries, the lower temperature of the skin is due not solely to occlusion of the main arteries but also to the additional factor of an excessive amount of vasospasm in the collateral arteries and arterioles. The test is carried out as follows: The patient is given foreign protein (typhoid vaccine) intraven-

ously, the surface temperatures of the hands and feet are estimated, and simultaneously the temperature of the mouth is recorded. During the period of chill there may be a fall in the surface temperature, but with the rise in the temperature of the mouth there is relaxation of the surface vessels and rapid increase in the temperatures of the skin; the difference between the maximal rise in the surface temperature and the maximal increase in blood (mouth) temperature constitutes the rise in surface temperature due largely to vasomotor effects. This value, divided by the number of degrees rise in temperature in mouth or blood, gives a value which, simply stated, represents the increase, in number of degrees, in the surface temperature for each de-



gree of increase in temperature of the body.

In cases of scleroderma it has been found that vasomotor indexes varied from 2.7 to 13.8, with an average value of 6.5. In the vasomotor forms of scleroderma, as a whole, there are slightly higher indexes than in the other forms of scleroderma (fig. 11). The indexes are not as high as those in cases of Raynaud's disease. This is to be expected, for reduction in cutaneous circulation in Raynaud's disease is due exclusively, we believe, to spasm. In scleroderma, there is the additional factor of occlusive disease of the smaller arterioles.

#### CLINICAL COURSE

The clinical course of three phases of scleroderma, with vasospastic disease of varying degrees, is presented in the following reports of cases:

CASE I (case 3, table 1, type 1): *sclerodactylia followed by symptoms of vasospastic disease*.—A man, aged thirty years, a machinist, came to The Mayo Clinic November 26, 1928. He had had the usual children's diseases, and had had erysipelas when he was aged fifteen years. Otherwise he had been well. In September, 1928, he had had pleurisy on the left side, and occasionally he had had pain on deep breathing. He had lost 16 pounds since the onset of the disease. Nothing was elicited in his family history or personal habits that was significant. In February, 1927, he had noted that his fingers were swollen and puffy in the morning. The swelling gradually had disappeared an hour or two after he rose from bed and his hands had remained normal until the following morning when the same course had repeated itself. Six months after the onset, the swelling had become constant during day and night, and had remained constant for several months. When the swelling had begun to subside, the patient had noted that his fingers were hard and stiff, so that he had been unable to clench his fist. This hardening of the skin

gradually had increased and had extended up the arm. At this time, about nine months after onset, he also had noticed that the fingers were sensitive to cold and when exposed to cold became blue. He was quite certain that they had not become white and only rarely had displayed a reddened phase. In December, 1927, about ten months after the trouble had appeared, he had noticed a similar process developing in the feet, and later in the face.

A diagnosis of Raynaud's disease had been made elsewhere in September, 1928, and treatment by roentgen rays had been given over the back, in addition to contrast mineral baths and "electric baths." In October, 1928, right cervical sympathectomy had been done elsewhere, following which his condition had not been improved.

When the patient was examined at the clinic the face was without wrinkles, had a waxy hue and imparted a sensation of firmness to the touch. Over the zygoma, the skin was so tight that it was impossible to "pick it up" like normal skin. The trunk, arms, and legs were hyperpigmented; some of the pigmentation, however, was the result of treatment by ultra-violet light. All the fingers were cold, waxy, stiff and smooth, and the skin seemed firmly attached to underlying structures. The skin of the palms was more flexible. The fingers were moderately flexed and could not be fully extended nor fully flexed. The skin of the forearm, and up to the lower third of the arm, also was thickened, firm, and waxy, but to a less degree than that of the hand. The toes appeared cyanosed and the skin of them was not so thickened as that of the arms. The blood vessels in both feet were patent. Examination of the thorax revealed a friction rub over the base of the left lung; otherwise the results of general examination were within normal limits. The blood pressure was 120 systolic and 75 diastolic, in millimeters of mercury, and the ocular fundi appeared to be normal. The tonsils were only slightly enlarged and contained plugs of inspissated pus.

Analysis of the urine and the blood count gave normal results. The Wassermann reaction of the blood was negative. Two apically infected teeth were demonstrated.

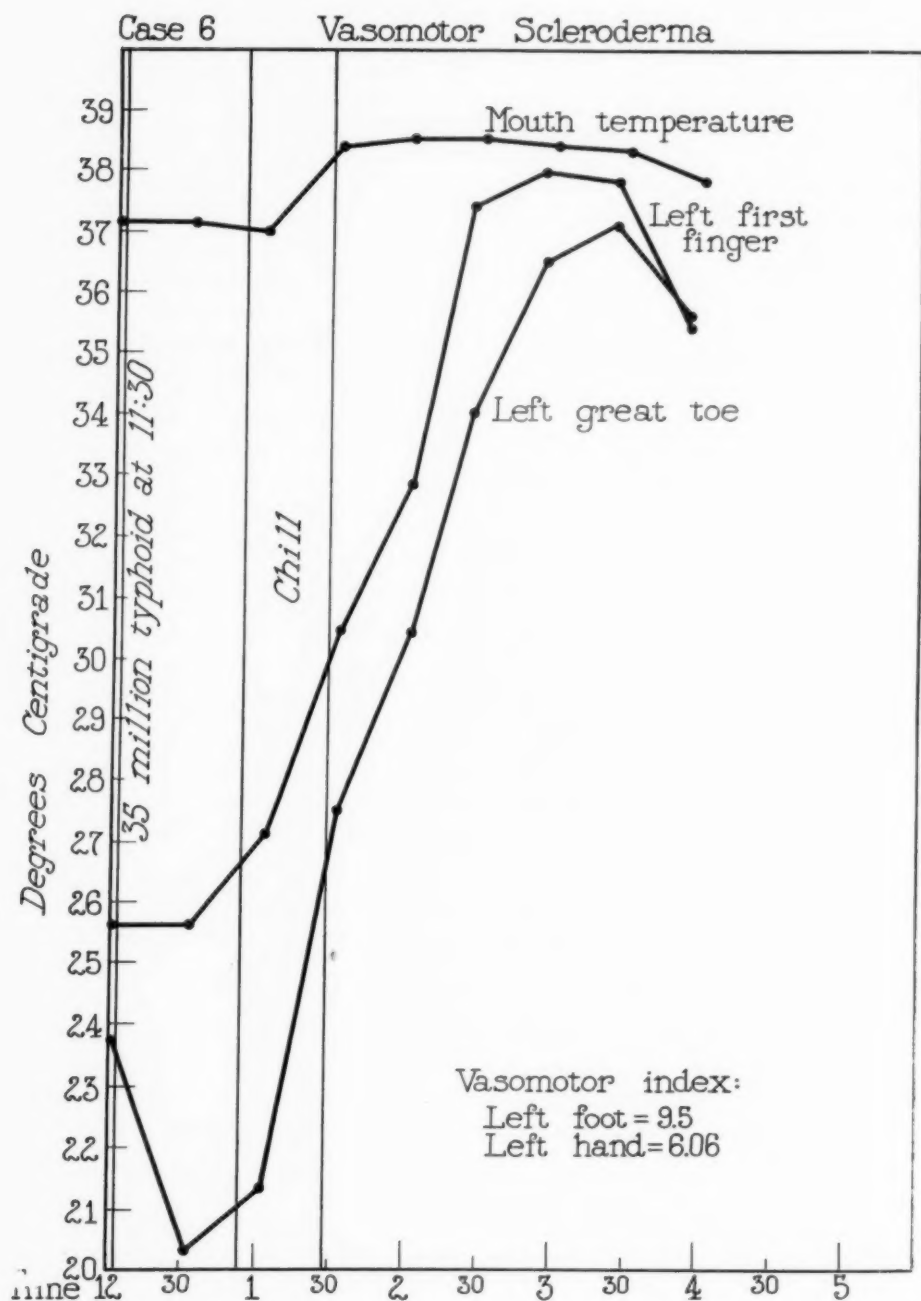


FIG. 11. (Case 6). Curve of the vasomotor index.

Roentgenologic examination of the hands disclosed partial destruction of the terminal phalanx of the right thumb, and of the thorax, nothing abnormal. The basal metabolic rate (DuBois standard) was  $+12$  per cent. The electrocardiographic report contained notations of sinus rhythm, aberrant QRS complexes, isolated derivation I, slurred right ventricular preponderance and a cardiac rate of 80 beats each minute. The vasomotor index in the right hand was 5.9, and in the left, 8.5. The surface capillaries were large and deformed, with a slow flow of cyanotic blood, typical of true scleroderma. The surface temperature in the right hand was  $27.1^{\circ}\text{C}$  and in the left,  $24.6^{\circ}\text{C}$ . Elimination of heat was estimated at 70 calories each minute.

A diagnosis was made of scleroderma with sclerodactylia and secondary vasomotor characteristics, for which resection of sympathetic ganglia and trunks was recommended.

December 11, 1928, Adson performed this operation in the left cervicothoracic region, and included the lower cervical and the two upper thoracic ganglia and the intervening trunk. It was thought advisable to postpone resection on the right side until the near future. When the patient was examined twenty-four hours after the operation, the left hand was warm and dry, but the right was unchanged. A Horner's syndrome was present on the left side. The second day after the operation, the skin of the left hand was decidedly softer than that of the right, and was of normal pink color. The veins on the left hand were fuller than those on the right and the color did not change materially with change of position. Definite parasthesia of the left arm was present.

January 8, 1929, a similar operation was performed on the right side; when the patient was ready for dismissal from the hospital, January 28, 1929 (seven weeks after the resection on the left side and three weeks after resection on the right), it was noted that the facial expression was different. The patient could wrinkle the forehead, pucker the mouth, and whistle much more readily. The sensation imparted to the fingers when palpation about the mouth was carried on was that the skin was loose rather than tight, as previously. The skin over the fingers was still stiff, although that on the fore-

arm and back of the hand was looser. There was no change in the mobility or flexibility of the hand. Hyperesthesia of both arms was still present, and considerable difficulty was encountered in the healing of the wound in the skin due to the influence of previous treatment by roentgen rays and of the sclerodermatous skin.

The result of the operation on this patient has not been satisfactory. Eight months after operation, he reported, by letter, considerable edema and pain in both upper and lower extremities.

CASE II (*case 4, table 2, type 2*); *sclerodactylia and vasospastic disease appearing simultaneously*.—A woman, aged fifty years, who worked as a charwoman, came under our observation in October, 1929, because of stiffness of the extremities. The remote history was irrelevant. She had three healthy children. She had undergone uneventful menopause three years before she came to the clinic. The essentials of her brief story were as follows: Approximately one year before we saw her she had noticed that her fingers became blue when they were exposed to cold but rapidly assumed the normal color when they were warmed. There had been no white or red stage and no pain of significance. About six months later she had noted swelling of the fingers and lower part of the legs, which was followed by stiffness of the skin of the hands and fingers. Approximately one month later, a similar sensation had appeared in the skin about the lower part of the face and neck, and also in the feet and lower half of the legs. Since then there had been gradual increase in the "stiffness" of the skin involved and extension up the arms and down over the shoulder girdle. Almost simultaneously with the onset of the scleroderma, numbness had developed in the fingers, associated with blanching and pain. Hyperpigmentation of the sclerodermatous areas had appeared three months before admission.

When the patient was examined, she seemed considerably younger than her years. Her face was almost wrinkleless and there was some decrease in the palpebral fissures. Ability to protrude the tongue was limited, due to restricted mobility of the jaw. The skin of the lower half of the face was

"tighter" than that of the upper half. The hands were held in a semiflexed position. Some healing excoriations were noted over the knuckles and the finger tips. The veins of the hands were not visible, and the hands were cold, wet, and "hard." The skin of the arms was firm and that over the upper part of the thorax had the characteristic sheen of scleroderma. The feet and legs also gave evidence of scleroderma of a less marked degree. Neurologic examination gave negative results.

The blood pressures were 110 systolic and 78 diastolic. Comparison of the patient's weight with what she said it formerly had been disclosed that she had lost 30 pounds since the onset of the disease. The urine appeared to be normal and studies of the blood disclosed mild secondary anemia. Roentgenologic examination of the thorax gave negative results. The basal metabolic rate (Du Bois standard) was +6 per cent. The vasomotor index of the right index finger was 8.1; of the right great toe, 6, and of the left great toe, 5.8. Elimination of heat in the right hand was 21 calories each minute; the surface temperature was 24.4° C. in the right hand and 26° C. in the left.

A diagnosis was made of scleroderma, with sclerodactylia and mild vasoplastic disease appearing simultaneously. Resection of sympathetic ganglia and trunks was recommended.

October 15, 1929, Adson performed bilateral resection of cervicothoracic sympathetic ganglia and trunks.

Convalescence was uneventful, and on dismissal from the hospital, October 24, the patient reported that her hands were decidedly warmer, the skin over the backs of the hands was looser and the hyperpigmentation was fading. However, she complained of numbness in both arms, which had persisted since the operation, and she was unable to open her mouth as wide as she had been able to open it previous to the operation. She presented a bilateral Horner's syndrome. Three months later she reported that the color of the hands was normal but they were still stiff. Her main difficulty was dryness of the throat, increase in stiffness of the feet, and some residual numbness in the arms.

CASE III (case 15, table 3, type 3); *vasoplastic disease preceding the development of sclerodactylia*.—An unmarried woman, a school teacher, aged forty-eight years, came under our care for the first time in June, 1922. She came with a diagnosis of Raynaud's disease. In 1912, periods had appeared during which the left ring finger was numb and there was definite blanching of the finger. The frequency of these attacks had increased, and soon other fingers had been involved. By 1917, five years after the onset of the disease, on exposure to cold all the fingers and toes first became white and cold, then blue, and finally red and warm. During this developmental period, the patient had noted that her fingers were becoming stiffer, a condition which was called to her attention particularly while she was dressing her hair. By 1920, the fingers had become stiff and "wooden-like"; involvement of the feet was much less. The patient emphasized the fact that the changes in color, and later on the stiffness in the fingers, both had been much worse during the cold weather. The stiffness of the skin of the face and thorax first had been noticed by the patient in 1921. During this developmental period a variety of therapeutic measures had been tried. Because a basal metabolic rate of +2 per cent had been noted in 1921, thyroid extract had been given, and in the spring of 1922, when the basal metabolic rate had been reported as -26 per cent, thyroid extract and thyroxin had been given until the rate had been raised to -11 per cent. As this had caused palpitation and precordial distress, the medication had been stopped, although the patient had felt somewhat improved. The use of ergot, suprarenal extract, pituitary extract anterior lobe, and nitroglycerine she said also had made her feel worse. During the year previous to admission to The Mayo Clinic she had noted that on exposure, such as that caused by undressing in a cold room, her skin had become blue and mottled, in irregular areas, and then flushed when she had become warm.

The patient was thin, with a pinched expression of the mouth. Although palpation of the skin of the face revealed little evidence of scleroderma, there was definite ironing out of wrinkles, and limitation of opening of the mouth. The skin over the thorax had a

definite shoen suggesting a slight degree of atrophy, but there was no palpable thickening. There was definite mottling of the skin of the trunk. The extremities, the hands in particular, were most markedly involved. The hands appeared waxy; the fingers were stiff and permitted of about 25 per cent flexion. The joints of the fingers were enlarged and tender to pressure. It was impossible to pick up the skin over the phalanges, although on the backs of the hands this could be accomplished with some limitation. The hands were cold and moist. A similar condition of the feet was noted, but to a much less degree. Also, palpable plaques, varying in size up to 5 mm., were noted along the peroneal tendons. When the fingers were exposed to cold water, or when they were hanging, they became cyanosed. The urine appeared to be normal. Secondary anemia was present as was shown by a concentration of hemoglobin of 67 per cent. Other factors of the blood count were within normal limits. The Wassermann reaction of the blood was negative. The basal metabolic rate (DuBois standard) was -7 per cent. The retinal vessels were tortuous, but otherwise the ocular fundus was normal. The search for foci of infection disclosed slightly enlarged and infected tonsils, and six teeth with apical infection. The cardiovascular and pelvic examinations disclosed normal conditions. The vasomotor index was not done but the surface temperature was 26.6° C. in the right hand, and 27.9° C. in the left.

It was suggested that the foci be removed, and that the patient continue with massage, following application of dry heat to the hands.

The patient returned for reexamination in 1926, four years after her first visit. Besides the original complaint, the chief trouble at this time was difficulty in swallowing; this was found to be due to a benign stricture of the esophagus, about 37.5 cm. from the central incisors. Vinson dilated the stricture frequently, and after prolonged observation he believed that it was not related to the scleroderma. At the time of the patient's second visit, the changes in the hands and face were more marked. The skin over the fingers and face was tighter, there was less motion in the fingers, and the patient was not

able to open her mouth as wide as before because the skin of her face was stiffer. Also, the joints of the fingers caused more pain, and rheumatism in the shoulders had developed. Roentgenologic examination revealed periarticular arthritis, with marked contraction deformity of the fingers. During the interval of four years since the patient's first visit to the clinic, she had received numerous intravenous injections of sodium thiosulphate without benefit. She had been treated also by the application of roentgen rays, massage and heat. Thyroid extract had been given and foci of infection had been removed but her condition had not improved. The similarity of the condition to Raynaud's disease was recognized at this time, and cervical resection of sympathetic ganglia and trunks was suggested, but was refused by the patient.

The following year, 1927, she returned, primarily for the esophageal stricture. There was no improvement in the scleroderma. In 1929, however, a decided increase in the severity and extent of the sclerodermatous involvement was noted. The degree of periarticular arthritis was more pronounced; in addition, roentgenograms disclosed atrophy of the bones of the hands. Small deposits of calcium also were noted in the finger tips. On the arms and upper part of the thorax there was now palpable hardening of the skin; the changes in color remained about the same.

June 18, 1929, bilateral resection of cervico-thoracic sympathetic ganglia and trunks was performed by Adson. On the seventh day after operation, a decided change in the facial expression was noted; the normal pink hue had replaced the previous waxy appearance, and the skin was decidedly softer. There was slight change in the capillary reactions over the anterior part of the thorax at this time. Horner's syndrome was present and equal on both sides.

On the fifteenth day after operation, the skin of the fingers, up to the first joints, was normal in appearance. All of the fingers were warm, but the mobility was not increased. The patient remarked that the "feeling of deadness and cold" had entirely disappeared. The tongue could be protruded further because the mouth could be opened



wider. The capillary reactions over the face and thorax had approached normal. The orbital fissures opened equally, but both pupils were contracted (Horner's syndrome).

A recent communication from the patient, seven months after the operation, stated that she had gained 10 pounds and that the most gratifying thing to her was that even though she was in a cold climate her hands had remained warm on the coldest days. The softening of the skin of the hands, which was noticed to a slight degree immediately after the operation, had continued to become more noticeable. Also the skin of the face and neck was much softer and had continued to improve. A number of superficial hemangiomas that had been present on the neck and upper part of the thorax also had disappeared. The only postoperative discomfort was pain in the right shoulder which developed after the arm was used for any length of time. She noticed it particularly after writing on the blackboard in her school work. Her hands were also "slippery" as a result of the extreme dryness.

#### PROGNOSIS

The expectancy of life of a patient with the generalized type of scleroderma is fairly long, not infrequently twenty years. The vasomotor type of the disease is likewise of long duration. We have not had the opportunity to study a case of scleroderma at necropsy and the literature contains but few data on observations at necropsy. The cause of death in scleroderma may be a terminal vascular disease or, more frequently, some intercurrent infection.

#### MEDICAL TREATMENT

There is no satisfactory medical treatment for generalized scleroderma. Because so many agents have been thought to be etiologic, the treatment has been varied. In the generalized type, thyroid extract has long been recommended. It is probable that the re-

lief obtained from the administration of thyroid extract is due to the vasodilating effect of the drug rather than to any specific influence on the thyroid gland. The use of massage following the application of heat has offered some help. In the group of cases reported by O'Leary and Nomland, only 6 per cent were materially benefited by treatment, in spite of the varied treatment. In a certain group of patients with the generalized form of the disease, there is spontaneous involution of the indurated skin; however, rather typical thin, atrophic scarring remains. This must be continually borne in mind in appraising the end-results in the treatment of scleroderma by any method. These few remarks on the inadequacy of treatment apply to the vascular type as well as to the diffuse forms of scleroderma. In those patients who are able to move to a dry, equable climate, such as that offered by the extreme southwestern part of this country, and who continue with massage, contrast baths, and supportive measures, the disease is of slower progress.

#### SURGICAL TREATMENT

*Theoretic Bases for Resection of Sympathetic Ganglia and Trunks in Cases of Vasomotor Type of Scleroderma.*—Clinical and thermometric observations convince us that sympathetic hypertonus of the arterioles is a significant element in the diminished vascularity of the skin in at least one group of cases of scleroderma. Whether or not the vasomotor disturbance is the primary agent in this type of case is not known. Much experience with this disease has convinced us that in this disorder the stage before the sclero-



derma is marked by vasomotor disturbances which simulate Raynaud's disease. This disturbance may antedate for years the onset of organic changes in the skin. The hypersensitiveness to cold, as expressed by the tendency to attacks of pallor and cyanosis, the frequent improvement of the patients when transported to warmer climates, the spontaneous improvement which may occur following some acute febrile reaction, and the temporary improvement which can be obtained by inducing fever by some nonspecific method, give impressive clinical confirmation of the fact that the vasomotor element is significant. The appearance and behavior of the capillaries of the skin demonstrate the pathologic hypertonus of the arterioles. Lowering of the temperature of the room by 2 to 3° will induce complete closure of the arteri-

oles, and cessation of the flow of blood in the capillaries. These studies impress the observer with the fact that the available circulation is tremendously impaired by this excessive tendency to spasm. Similar evidence is afforded by the fairly high vasomotor indexes.

Surgical measures applied to the sympathetic apparatus, that now are available<sup>1,5</sup>, permanently interrupt the vasomotor pathways to the vessels of the hands and feet. The fact that cases of Raynaud's disease, selected cases of thrombo-angiitis obliterans, and cases of other disturbances associated with vasospastic disorders respond most satisfactorily, is ample basis for utilizing the operative measures in the cases of scleroderma in which the vasomotor element seems to be the primary, and perhaps the major, disturbance.

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## Surgical Treatment of Vasospastic Types of Scleroderma by Resection of Sympathetic Ganglia and Trunks\*

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THE permanent vasodilator effect following resection of sympathetic ganglia and trunks, with its subsequent physiologic changes, has stimulated us to find numerous clinical applications of the procedure. Naturally any disease that arises either directly or indirectly from impaired circulation must be considered. The results obtained by interrupting the vasoconstrictor fibers of the peripheral arteries are determined by the dilatation of the arteries and arterioles affected by the operative procedure. Therefore, it is extremely important to select patients who have nonocclusive lesions of the arteries, and who have vasomotor spasm of the arteries which has resulted in impairment of the circulation. Little, if anything, is to be accomplished by performing resection of sympathetic ganglia and trunks in cases in which there are destructive

changes in the walls of the arteries, such as are found in arteriosclerosis, since these vessels are incapable of dilatation even though the vasoconstrictor fibers are cut. Furthermore, nothing is to be accomplished by the operative procedure if the disease has progressed to such an extent that the arteries have become obliterated by late fibrous changes.

Raynaud's disease is the classical disorder which results from vasospasm, and is the one that has responded most favorably to interruption of the vasoconstrictor fibers. Thrombo-angiitis obliterans also falls into this category of vasospastic diseases, inasmuch as the collateral arteries are the site of marked vasomotor spasm, even though there is an occlusive lesion of the principal arteries and veins. The result of the operative procedure, in thrombo-angiitis obliterans, is dependent on the degree of spasm of the collateral vessels; the greater the spasm, the greater its release by the operation, with concurrent improvement of the circula-

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tion. In turn this means relief of pain, reduction in edema, healing of ulcers, and restoration of function to the extremity.

In view of the results obtained in the treatment of Raynaud's disease and thrombo-angiitis obliterans, it was apparent that resection of sympathetic ganglia and trunks might be applied to a type of scleroderma involving the skin over the fingers, hands, forearms, toes, feet, and legs, as well as that covering the face, neck, and upper part of the thorax. This type of scleroderma apparently develops as a result of vascular disturbance in persons who have complained of cold, wet, clammy hands and feet. In a few instances, the cutaneous changes came on suddenly, but more often they were preceded for many years by what may be called mild Raynaud's disease. In attempting to explain the sclerotic changes that develop in scleroderma, it is found that the vasomotor spasm is of milder degree than that in Raynaud's disease, but that it is more continuous. Therefore the periods of thorough relaxation of the arteries in Raynaud's disease are probably sufficient to bring about restitution of the injury that has taken place during the stage of asphyxia. Hence the changes of scleroderma are not seen in true Raynaud's disease. The ulceration that takes place in Raynaud's disease probably is the result of sudden, severe constriction of terminal arteries, which do not relax sufficiently during the phase of dilatation to bring about recovery.

Curiously, the sclerodermatous changes were more pronounced in the skin of the hands, neck and face than

they were in the skin of the feet. This was probably due to the fact that the existing vasomotor spasm was aggravated by exposure to environmental changes; therefore, one would expect the disease to be more advanced in the uncovered parts of the body, such as the hands, than in the protected parts of the body, such as the feet.

#### EVALUATION OF OPERATIVE RESULTS

This review includes a group of sixteen patients, in all of whom bilateral resection of cervicothoracic sympathetic ganglia and trunks was performed through the posterior approach. In three patients, bilateral resection of lumbar sympathetic ganglia and trunks had been performed in addition to the operation in the cervicothoracic region. The scleroderma was of the moderately diffuse type, and affected the skin of the hands, the arms, the face, the neck, the scalp, the anterior portion of the thorax, the feet and the legs.

The patients were divided into three groups, classified on the basis of the relationship of vasospastic phenomena to the development of the disease: group 1, primary scleroderma, vasomotor disturbance appearing late in the disease, table 1; group 2, simultaneous development of scleroderma and vasomotor disturbance; table 2, and group 3, vasomotor disturbance preceding the development of scleroderma, table 3.

*Group 1; cases 1, 2, and 3.*—Definite changes were noted following operation. The symptoms of vasomotor reflex disappeared; the skin became warm and softer or more flexible;

TABLE I. EFFECTS OF RESECTION OF CERVICOTHORACIC GANGLIA AND TRUNKS ON SURFACE TEMPERATURE AND ELIMINATION OF HEAT IN HANDS.

Case	Surface temperature of fingers* degrees centigrade				Elimination of heat in hands**		Time after operation when records were made, days
	Before Operation		After operation		Before operation	After operation	
	Right	Left	Right	Left			
1	24.8	25.6	28.7	29.1	15	76	Right side, 52 Left side, 19
2	25.0	25.3	33.6	33.5			12
3	27.1	24.6	29.4	28.8	70	140	Left side, 62 Right side, 35
4	24.4	26.0	32.1	32.2	21	33	9
5	24.7	24.7	32.5	32.9	45	70	19
6	25.6		29.1		27	80	28
9	23.8	22.8	28.1	29.0			40
10	21.7	19.6	27.8	28.5			16
11	24.5	24.5	31.1	27.7	18	78	35
12	27.2	26.7	31.6	30.8	32	47	13
15	26.6	27.9	31.7	31.9	45	72	71
16	29.8	28.8	30.7	29.5			35
Mean values	25.4	25.1	30.5	30.3	34	74	

\*Average of fingers of both hands.

\*\*Small calories of heat eliminated for entire hand and number for unit area.

pigmentation diminished; mobility of the joints increased; muscular function developed; trophic ulcers healed, and growth of the hair and nails took on new activity. Postoperative study of this group has been limited for the most part to convalescence in hospital, which has not given sufficient time to make final estimations, but it is doubtful if the ultimate results in this advanced group will compare favorably

with the gratifying results obtained in group 3.

*Group 2; cases 4, 5, 6, and 7.*—The symptoms, in this group, progressed more rapidly than those in group 3, and were somewhat similar to those in group 1. There was marked fibrosis which was not altered greatly by sectioning of the vasoconstrictor fibers. Postoperative changes in this group were similar to those in group 1. Suf-

TABLE 2. EFFECT OF INDUCED FEVER AND OF OPERATION ON SURFACE TEMPERATURE.

Temperature in degrees centigrade						
Case	Hands, with normal body temperature	Induced rise in body temperature	Hands, after fever had been induced.	Hands, rise due to vasomotor effects	Hands, rise due to operation	Vasomotor index before operation
1	27.1	2.5	36.6	7.0	3.7	2.7
2	23.5	1.6	36.8	11.7	9.2	7.3
3	24.1	1.9	36.0	11.9	8.8	7.3
4	23.0	1.6	37.6	13.0	8.5	8.1
5	28.9	1.7	37.4	6.8	7.6	4.0
6	25.7	1.6	38.0	10.7	4.9	6.6
9	22.8	2.0	34.7	9.9	5.1	6.7
10	21.7	0.8	33.6	11.1	7.8	13.8
11	28.6	2.7	38.7	7.4	5.0	2.7
12	26.4	1.6	34.6	6.6	4.1	6.6
13	27.8	1.2	36.8	7.8		6.5
14	25.9	1.6	37.8	10.3		6.4
Mean values	25.5	1.7	35.6	9.5	6.5	6.5

cient time has not elapsed to give final evaluation of the operative results.

*Group 3; cases 8 to 16.*—In the nine cases of this series, the disease had been present for from five to twenty-two years. All patients underwent resection of cervicothoracic sympathetic ganglia and trunks and, in cases 9, 11, and 13, bilateral resection of lumbar sympathetic ganglia and trunks also was performed. In case 9, the resection in the lumbar region was performed twenty-six months before that in the cervicothoracic region. The most impressive improvement was noted in the feet after this lapse of time. The scleroderma had disap-

peared entirely. The feet were warm and dry, and the patient stated that so far as she knew, they were perfectly normal. The only untoward effect of the operation was the extreme dryness in the feet and the tendency to abrasions of the skin over the malleoli from friction of the shoes. For the group as a whole, the percentage of improvement of the condition of the upper extremities varied from 30 to 60 per cent within the period of post-operative observation. The improvement in the condition of the feet in the other two cases in which the lumbar operation had been carried out was greater than that obtained in the hands.



TABLE 3. RESULTS OF OPERATION IN RELATION TO TYPE AND DURATION OF SCLERODERMA

Case	Age, years, and sex	Duration of disease, years	Percentage improvement with resection of cervicothoracic ganglia and trunks*	Type of scleroderma in relation to vasomotor disturbance
1	37 M	1.25	5-10	Primary scleroderma with late vasomotor disturbances
2	41 M	1.5	10-15	Primary scleroderma with late vasomotor disturbances
3	30 M	2	10	Primary scleroderma with late vasomotor disturbances
4	50 F	1.5	10-15	Vasomotor disturbances and scleroderma developing simultaneously
5	55 F	2	20	Vasomotor disturbances and scleroderma developing simultaneously
6	19 F	2	30+	Vasomotor disturbances and scleroderma developing simultaneously
7	34 M	3.5	30	Vasomotor disturbances and scleroderma developing simultaneously
8	24 M	5	30-40	Vasomotor disturbances preceding development of scleroderma
9	32 F	5	50	Vasomotor disturbances preceding development of scleroderma
10	36 F	5	60	Vasomotor disturbances preceding development of scleroderma
11	34 M	8	30	Vasomotor disturbances preceding development of scleroderma
12	35 F	11	50	Probably a vasomotor form; slowly progressive scleroderma
13	37 F	13	40	Vasomotor disturbances preceding development of scleroderma
14	44 F	15	35	Vasomotor disturbances preceding development of scleroderma
15	57 F	17	40	Vasomotor disturbances preceding development of scleroderma
16	25 F	22	30	Vasomotor disturbances preceding development of scleroderma

\*The results of resection of cervicothoracic ganglia and trunks were estimated at periods of two weeks to five months after operation, and the opinion given was based on the statements of each patient and of at least two physicians. Similar methods were used in estimating the benefits of resection of lumbar ganglia and trunks in the three cases (9, 11 and 13) in which it was done, except that in case 9 the estimation was not made until twenty-six months after operation. In case 9, the percentage of improvement was estimated as 90; in case 11, 80, and in case 13, 80 to 90.

although complete involution of the sclerodermal process, such as that in case 9, was not noted. However, we are of the opinion that, as time elapses, further improvement will take place. In those patients who were observed for longer periods of time after operation, regression of the cutaneous thickening was continuing. Thermometric studies in this group were carried out in six cases. The average surface temperature of the fingers of the right hand was  $25.3^{\circ}\text{C}.$ ; following operation it was  $30.9^{\circ}\text{C}.$ ; the mean increase for the group was  $5.6^{\circ}\text{C}.$  For the fingers of the left hand, the mean value for the surface temperature before operation was  $25.2^{\circ}\text{C}.$ ; after operation it was  $31.3^{\circ}\text{C}.$  The rate of loss of heat in the hands before operation, in three cases, was 32 small calories, and after operation, 66 small calories for each minute.

The improvement in the cases of group 3 was fairly decisive from the standpoints of clinical observation, patients' statements, subjective improvement, and studies of temperature. (Figs. 1 to 4). Improvement in the cases with fairly long periods of observation was progressive and continuous. Further information on the improvement in this group is afforded by the fact that the number of patent capillaries for each unit area of skin was increased. The capillary flow was accelerated, the blood was of a normal reddish color, and hypertonic disturbances of the arterioles were greatly lessened or had disappeared.

Considering the improvement in the group as a whole, this study of a comparatively small series of cases indicates fairly conclusively that the dura-

tion of the disease and the early vasomotor disturbances are important in the predicting of results from this operation. The high degree of improvement of the condition of the feet, in these cases, is probably due to two factors: (1) the effect on vasodilatation of resection of the ganglia and trunks is more complete in the feet than it is in the upper extremities, and (2) when the disease is present to a marked degree in the upper extremities, the condition in the feet is less advanced; the organic changes are not advanced. Involution and possibilities of cure would be anticipated on this basis.

#### OPERATIVE TECHNIC

Leriche, in attempting to treat scleroderma by interrupting the vasoconstrictor fibers, first performed periarterial sympathectomy, on the basis that the innervation of the artery was centrifugal in origin. Later it was his impression that there probably existed a centripetal innervation; this, also was disproved; he then held that there probably existed an intramural sympathetic ganglion, the removal of which would produce relaxation of the artery below the site of operation. However, the work of Kramer and Todd, and Potts has proved rather conclusively that the vasoconstrictor innervation is distributed to the artery at various levels corresponding to the cutaneous and somatic segments. Hence, if it were hoped to accomplish relaxation of vessels, it would be necessary to interrupt the sympathetic vasoconstrictor fibers at some point above their entrance into the spinal nerves. This clearly indicated ramisection, or ganglionectomy and resection of trunks.

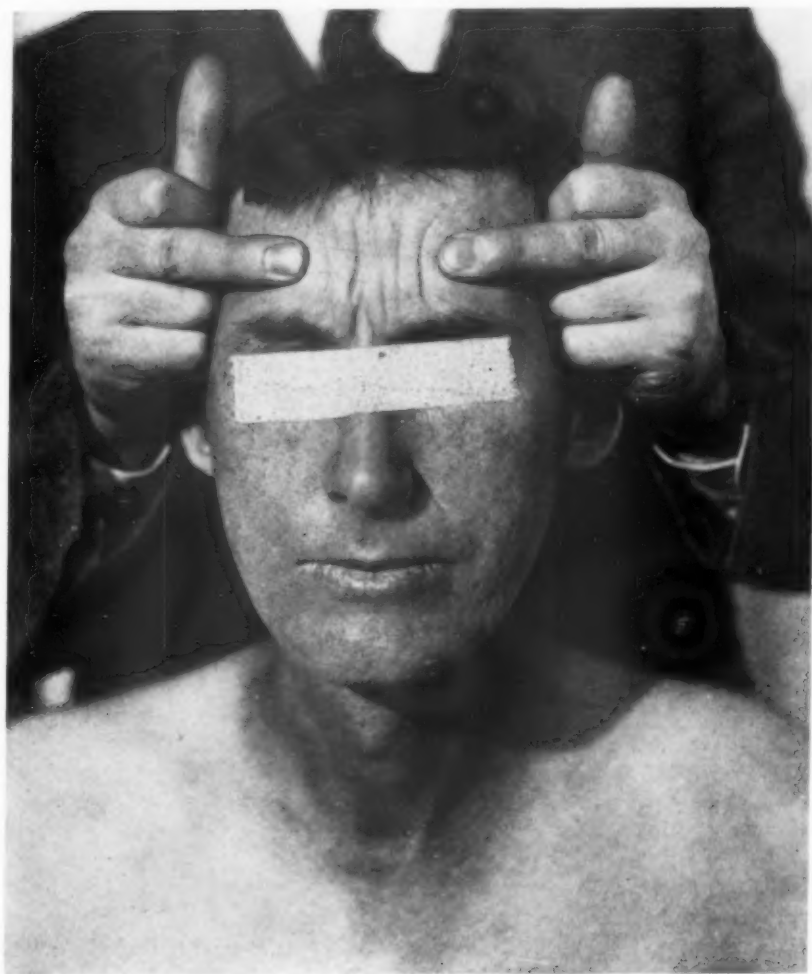


FIG. 1. The hide-binding of forehead before operation.

Our experiences in the treatment of Raynaud's disease of the lower extremities taught us that if we were to accomplish thorough relaxation of the vessels, it was necessary not only to divide rami, but to resect the lumbar ganglia and the sympathetic trunks, since the distribution of the rami is so irregular that they are easily overlooked. By resecting the lumbar trunks above the second lumbar gang-

lion and below the fourth lumbar ganglion, and removing the intervening ganglia, we were able completely to interrupt all vasoconstrictor fibers going to the arteries of the lower extremities. A similar procedure, therefore, was carried out in the treatment of scleroderma of the feet and legs. We did this October 17, 1927, with excellent results, which consisted in relief of pain, improvement in circula-

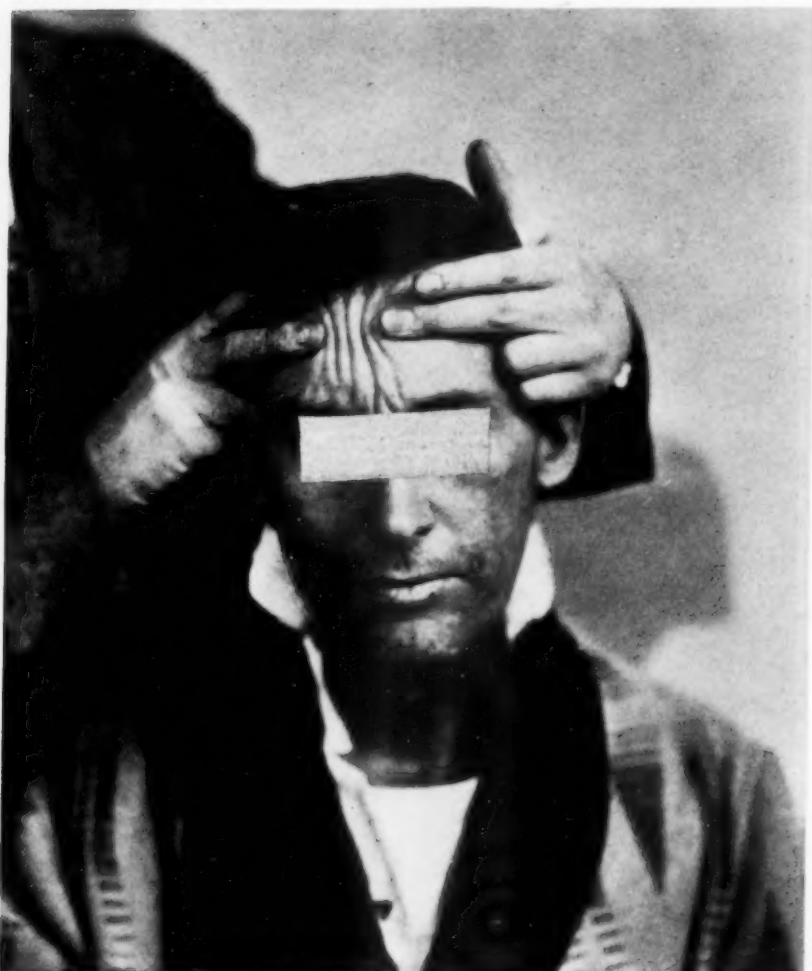


FIG. 2. The skin of forehead is more easily wrinkled as a result of the softening. Photograph taken fourteen days after operation.

tion, partial restoration of the skin to its normal state, and partial recovery of muscular function. The patient is now free from all complaints due to exposure to cold. She has complained of her feet being too warm during hot weather, but said that they are not warm enough to be troublesome. The skin is dry, because of the interruption of the sympathetic fibers to the sweat

glands, and is rather thin over bony prominences. New vessels have grown into the atrophic regions, as can easily be demonstrated by simple observation and by compressing the skin. The muscles of the leg have again taken on their normal size and present the fusiform appearance of normal muscle. The function of the lower extremities has been completely restored.

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FIG. 3. The induration of skin is demonstrated by the difficulty in wrinkling.

At the time of her first operation, the patient had a more aggravated form of sclerodactylia of the upper extremities with involvement of the skin and muscles of the upper extremities, face, and neck. However, inasmuch as we had not perfected an operative procedure for thoroughly interrupting the vasoconstrictor fibers, which supply this region, the patient was compelled to return home. Since then she has returned to us and on October 29, 1929, submitted to the newer procedure of resection of cervicothoracic sympathetic ganglia and

trunks, through the posterior intrathoracic approach.

This patient gave us an excellent opportunity to study the results of operation on the lower extremities in comparison with the progress of the disease in the upper extremities, which had not had the benefit of operation. It became obvious that, unless something is done to relieve the vasomotor spasm, which apparently is the underlying factor in the production of this particular type of scleroderma and myositis with atrophy, the disease will progress, producing fibrosis of the



FIG. 4. The skin is now readily picked up by fingers of one hand.

skin, subcutaneous tissue, ligaments, fascia, and muscles. Finally ulceration takes place over the bony prominences and complete invalidism ensues.

This same patient, following resection of cervicothoracic sympathetic ganglia and trunks, began immediately to improve. The skin became warm, giving evidence of arterial relaxation and increased blood supply to the skin over the fingers, hands, arms, thorax and face. Relaxation of the skin was taking place at the time of the patient's dismissal, and strength was returning to the muscles of the hands,

forearms, arms, and the masseter muscles. Relaxation of the masseter muscles was taking place, and the patient was able to open her mouth wider than before the operation. Relaxation of the muscles of the tongue likewise was taking place, so that she was able to extrude the tongue farther than before the operation. On the whole, it appeared that recovery would take place in the skin and the adjacent tissues of the upper extremities similar to that which had taken place in those of the lower extremities.

Brüning reported success in the treatment of Raynaud's disease and



scleroderma of the upper extremities by resection of the stellate ganglion through the anterior superior approach. Although it is possible to get such a result occasionally by the procedure described by Jonnesco, it is usually met with failure; Kuntz has shown that removal of the so-called stellate ganglion, by the anterior approach, does not interrupt all of the sympathetic vasoconstrictor fibers to the arteries of the hands. Therefore, a surgical procedure was proposed and carried out, which consisted in a posterior intrathoracic approach, which would permit resection of the thoracic trunk, below the second thoracic ganglion, with complete removal of the lower cervical and first and second thoracic sympathetic ganglia, with the intervening trunk. This was done by resecting the proximal portion of the second rib, with the transverse process of the second thoracic vertebra and thus opening the thoracic cavity on each side of the spinal column. But again difficulty was encountered, because occasionally the lower cervical ganglion was a circumscribed structure, separated from the first thoracic ganglion, but communicating with it through the sympathetic trunk. In such cases the lower cervical ganglion could not be delivered into the wound and could not be satisfactorily resected. The result was that the Horner's syndromes were unequal, and that occasionally areas which perspired still existed on the hands. This suggested, of course, that some sympathetic vasoconstrictor fibers had entered the upper portion of the lower cervical ganglion the lower part of which had been resected. The remain-

ing upper portion, in turn, had sent fibers on to the ciliary ganglia and to a localized area on the skin over the hand. The procedure was then changed and the thorax was entered through an opening made by resection of the first rib instead of the second, thus permitting exposure of the first sympathetic thoracic ganglion between the eighth cervical and the first thoracic nerves. Then it was possible to bring into the wound, with ease, and to resect the lower cervical, the first thoracic, and occasionally the second thoracic ganglia, with the intervening trunks. In case the second thoracic ganglion was low-lying the first thoracic nerve was thoroughly dissected free from all communicating rami and fibers, from the intervertebral foramen to its juncture with the eighth cervical nerve to make up the lower trunk of the brachial plexus. Thus, all white rami, as well as all gray rami extending upward from the two upper thoracic ganglia and nerves, and the trunk which carries rami to the upper cervical ganglion were interrupted. This procedure, which we have carried out many times in these varied peripheral vascular diseases, has given evidence of interrupting completely all sympathetic fibers above the second thoracic nerve, with the result that the Horner's syndrome is always bilateral and complete on both sides, and that no areas of perspiration remain on the skin of the face, neck, arms, or hands.

#### LIMITATION OF SURGICAL TREATMENT

In the late stage of the disease there is marked increase of the collagen in the corium, which interferes with the

flow of blood in the superficial vessels. Because the blood vessels with the lowest pressure, such as the venules and capillaries, are compressed, they become distorted, and obstruction of the blood supply is produced. In addition to this compression, there is definite evidence of obliterative disease in the arterioles and consequent thrombosis of the vessels. As a result of these two processes, there is atrophy of the appendages of the skin besides trophic ulcers and destruction of the finger tips. It is evident that these changes will not undergo involution by medical or surgical treatment; accordingly, in the selection of cases for operation, it is important that surgical treatment should be carried out as early in the disease as possible. It appears to us most unlikely that vasodilatation, if produced in the late or advanced stage of the disease, will produce impressive degrees of improvement. In spite of these deductions, surgical treatment may be justified in advanced cases because of the symptomatic relief obtainable, and because of the inadequacy of any other type of treatment.

We feel it essential to discuss the problem frankly with the patient, so that he will clearly understand the probable degree of improvement to be obtained. In view of the fact that the ultimate prognosis in the majority of these cases is extremely grave, that the condition is usually progressive, and that deformities develop, one is justified in stating clearly to these patients that the smallest amount of improvement is worth having. When arthritis and flexion deformities are present, improvement will not be complete, and

physiotherapeutic treatment should follow surgical measures. It is not possible to predict the effects on the skin from increasing the circulation, for this depends on the amount of vascular occlusion present, and only careful study of the changes after operation in cases representing different forms of the disease would answer this question.

#### POSTOPERATIVE SEQUELAE

The increased temperature of the skin which follows the operation is a prominent manifestation, but is not troublesome; the patient may sleep with the extremities uncovered. He may complain, during the hot weather, of itching. This is probably due to the dryness of the skin which is a result of the operation, since the fibers to the sweat glands run with the vasoconstrictors and must perforce be divided with the vasomotor nerves. The dryness and itching are readily relieved by oiling the skin with lanolin or coconut oil. The vasodilatation does not produce the symptoms of erythromelalgia. The Horner's syndrome must be accepted if complete interruption of vasomotor nerves of the upper extremities is to be effected. A unilateral Horner's syndrome is a disfiguring and annoying phenomenon, but a bilateral one is rarely complained of.

We have encountered difficulty in the healing of the surgical wound in four cases. On removal of the sutures at the time usual for other lesions, the edges pulled apart, and there was little evidence of any healing having taken place. In two cases, we resutured the thoracic wound three times, and finally had to let it granulate from the

muscular layer, which always healed. This trouble is now overcome by using long tension sutures of silkworm-gut which are left in place until healing has taken place.

Following operation in advanced cases, the patients have experienced pain in the large muscles of the included region. This manifests itself in about a week after operation, is severe for two or three weeks, gradually diminishes in severity, and disappears in eight or ten weeks. It apparently is due to the engorging process that takes place in the vessels throughout the muscles, following the vasodilation.

A few patients have complained of localized tenderness, for a short time, along the brachial nerves. At first we suspected this might be due to trauma of the eighth cervical and first thoracic nerves during the operation, but when other patients did not have such pain after operation, we had to look for another explanation, and concluded that it is due to the process of revascularization, since the pain always disappears as recovery takes place. Exhaustion is a pronounced symptom in this group, and the greater the exhaustion before operation, the longer time is required for recovery from it following operation.

#### SUMMARY

It has been our purpose to call attention to a group of patients who

have complained chiefly of scleroderma affecting the skin of the hands, arms, face, neck, feet and legs, and in whom this condition is related to a vascular disturbance manifested by chronic hyperactivity of the sympathetic nerves supplying these regions. At the onset, these patients have complained of cold, clammy, wet, and cyanotic hands and feet, followed by swelling, hyperpigmentation and pain. Subsequently, as a result of the cutaneous sclerosis, there is tightening and hardening of the skin. Weakness and atrophy of the muscles ensue, with deformity and ankylosis of the phalangeal joints. Resection of the sympathetic ganglia and trunks has been advocated and carried out in this group, with the purpose of improving the circulation by relieving the vasomotor spasm, and thus dilating the arteries and arterioles.

The surgical results depend on the vascular relaxation accomplished. Hence it is important to make a careful selection of patients who present vasospastic phenomena. It is unwise to operate in the advanced cases, which fail to respond favorably to the vascular tests. It is obvious that operative procedures should be instituted early in the course of the disease in the phase in which the condition resembles that in Raynaud's disease, in order to check the disease and improve the existing symptoms.

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## The Relation of Endemic Goiter to Mental Deficiency

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ENDEMIC goiter has occupied a prominent place in medical literature from the time of our earliest medical writings. We also find references to this age old disease in our ancient manuscripts.

We have definite records of cretinism since early Roman history, but it was not until the beginning of the 16th century that the Swiss physician, Paracelsus, described cretinism in detail and emphasized the relation of cretinism to endemic goiter. In 1800, appeared Fodere's basic essay on "Goiter and Cretinism", in which he states that "Goiter is the first degree of a degenerative process in which cretinism is the last step." Again we have the French physician, Morel, expressing this same relation in the statement "Goiter is the first step on the road that leads to cretinism." Throughout the last half of the 19th century we have many volumes dealing with endemic goiter, cretinism, deafmutism and certain types of congenital feeble-mindedness, with definite impressions that the primary cause of all of these conditions is the same.

The scientists of Europe early recognized the intimate relation of goiter to mental deterioration and their governments foresaw the tremendous social responsibility of this disease. A com-

mission to study every phase of endemic goiter was appointed by the Sardinian government in 1848, and by the French government in 1864. In 1908 the Swiss government appointed a goiter commission, and in 1915 the Italian government took similar action.

In our mildly endemic districts we were not at first greatly impressed by the possibility that many cases of mental retardation were due to endemic goiter; but with each survey through our school population, it became more evident that a great many children with congenital goiter showed nervous and mental defects which in some cases resembled mild cretinism. In the study of large numbers of goitrous children, one saw every grade of mental deficiency from the slightly subnormal to cretin idiocy. In some cases, the etiology of the mental status seemed obvious, but in the majority it required a careful study of the family history, of the condition of the mother during pregnancy and of the entire life of the child, before an accurate estimate of the relation of the mental deficiency to congenital hypothyroidism could be made. To clarify this relation is the purpose of this study.

In 1924 the Michigan State Department of Health made a survey of all the school children in four counties.

The counties were so located as to give a fairly accurate cross section of the goitrous conditions throughout the state. In this survey all boys and girls from the first to twelfth grades were included and a total of over 36,000 were studied. In each of the four counties, the children were divided into the goitrous and non-goitrous, and the data of each county showed that ten per cent more goitrous children than non-goitrous were on the delinquent list. In this survey we did not have mental tests and rating to determine the delinquency, but if a child had been held back one or more grades he was classified as mentally retarded and this same mental retardation was found more frequently among the goitrous than non-goitrous. We now know that many cases of mental deficiency among those classed as non-goitrous were due to a maternal hypothyroidism during the congenital life of the child without affecting the thyroid sufficiently to produce a palpable goiter. Therefore, the thyroid was diagnosed as normal and the child classed as non-goitrous.

In 1925-26 we studied all the children of six counties in Ohio and exactly the same conditions were found as throughout Michigan. During this study of 56,000 children we were greatly impressed by the frequency of the number of cases in whom we had found mental retardation and congenital goiter. The mental rating was not reported in many of the schools, therefore, we cannot report definite data from this survey. However, this etiological relation of endemic goiter to subnormal mentality impressed us so strongly that the researches herein re-

ported were undertaken in order to obtain accurate data on this point.

During the summer of 1928 the research committee of the school board of the Detroit public schools decided to make a special study to correlate the physical and mental condition of each child in the subnormal classes. The enrollment of their special schools was more than 4,500 at that time, and increasing faster than they were prepared to care for them. They thoroughly appreciated the fact that the equipment of more special schools for this group was not the final answer. Therefore, a plan was evolved to study each child of this special class, determine the cause of the mental deficiency, and to treat the condition where possible. What was considered most important, however, was to find some method to prevent the conditions responsible for the mental delinquency. It was the opinion of the committee that in many cases some glandular disturbance was responsible for the abnormal mental growth, and to determine the facts on this point each child was studied primarily for endocrine dysfunction. This investigation began in October, 1928, in cooperation with the Departments of Special Education and Psychologic Clinic of the Detroit schools. Most of the routine physical examinations in the clinic were made by Dr. Marinus and the first studies in the school for the detection of endocrine problems were made by myself.

For obvious reasons a thorough examination of the children in the school could not be made. In fact we did not ask or claim to make an examination, but called it only an inspection. For this inspection, we had before us a card



giving chronological and mental age, weight, height and his previous health examination by the regular school physician. This showed his rate of growth and any defects of sight or hearing; we also had their findings on chronic infection, teeth, goiter, anemia and posture. Our inspection included size, body proportion, fat distribution, posture and any bony defects; also texture of skin, hair and nails. We examined teeth and thyroid carefully in every case. By this method the cases for further endocrine study at the clinic were selected and this study group averaged twenty per cent of the total number inspected in the school. Our completed study shows that seventeen percent of the children of the special schools suffer some endocrine dysfunction. Whether this dysfunction is the basis of the abnormal mental growth, is the question that this investigation is meant to answer.

Each study case was brought to the clinic by the mother. This is important, for inspection of the parent is most helpful in the final diagnosis. Our study here started with the mother, her condition during pregnancy and history of goiter; then the birth history and early life of the child; the age of teething, walking and talking; early childhood diseases and nutritional disturbances. At this time, a careful examination is made with the child stripped, with measurements of trunk and extremities for body proportions. In the boys development of the genitals is noted.

We assumed that any endocrine disturbance which was sufficient to cause mental retardation would also leave some mark on the child's physical de-

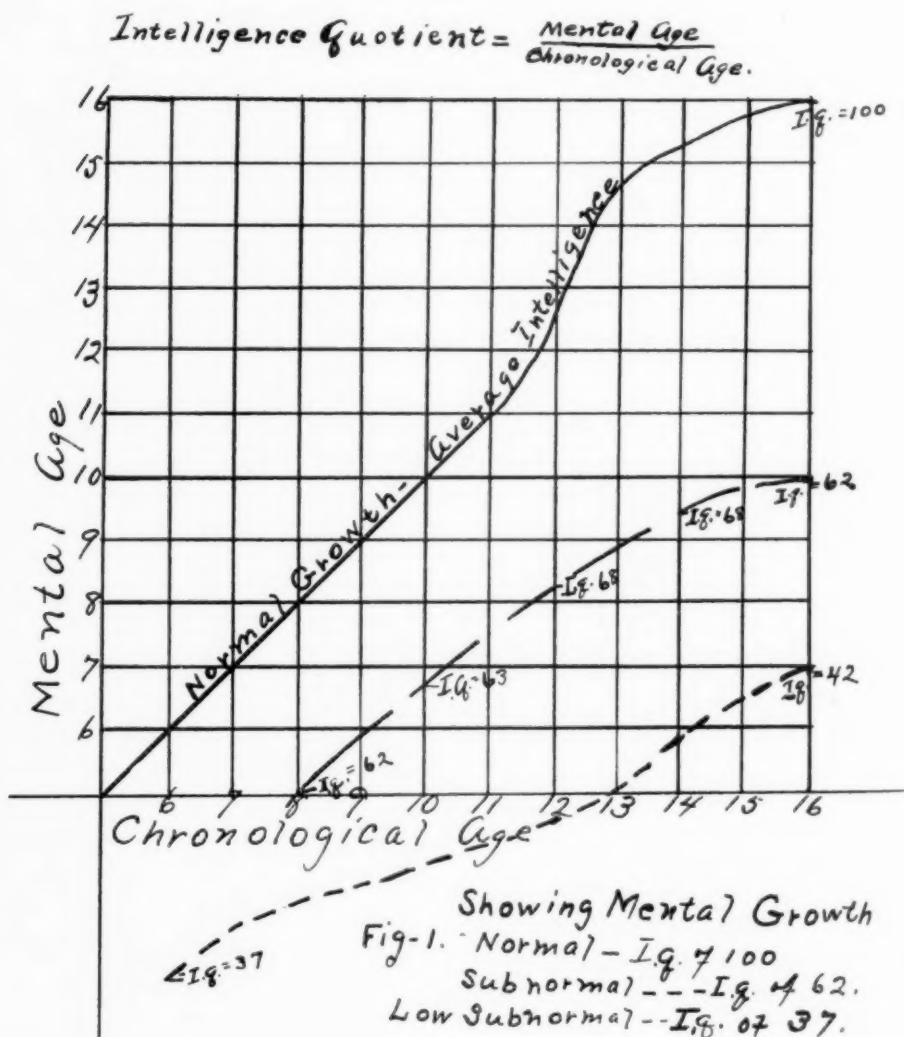
velopment. Therefore, our diagnosis was made from clinical study with the aid of such laboratory tests as basal-metabolism, blood-count, blood-Wassermann and in a few cases x-ray.

This investigation during the past two years includes 3,548 mentally subnormal children. Of this number, 712 showed some endocrine dysfunction, approximately seventeen percent. A similar study through the Detroit schools in 1922 by McGraw showed twenty-four percent with endocrine problems. Of these 712 endocrine problems, 281 are definitely the result of congenital hypothyroidism; or eight percent of all mental defectives of the Detroit schools are due to endemic goiter. If studies from the state institutions were included, ten percent of all the feeble-mindedness would be found to be the result of endemic goiter. In countries where endemic goiter is more severe and the condition has existed throughout generations, as in Switzerland, the number of feeble-minded due to it creates a real social problem. We do not need further proof that the mental status of the 2,000 cretins of the city of Berne is the direct result of endemic goiter; but its responsibility to the 4,500 subnormals of Detroit is not quite so obvious. Yet I am certain that in our mildly endemic districts many of the children classed as subnormals are as definitely related to endemic goiter as our cretins. They are defective because of a maternal hypothyroidism during their congenital life. The severity and duration of the hypothyroidism and the age of the child determines the relative damage.

Of the 281 cases diagnosed as congenital hypothyroidism, 205 have had

repeated intelligence tests so that one can study their mental growth. Ninety, or forty-four percent of these 205, approach the normal rate of growth. They maintain a constant intelligence quotient, but always below normal. A typical example of this group is shown by the graph in Fig. 1. A child of eight years has the mental age of a child of five years or an I. Q. of 62. At sixteen years he still has an I. Q. of 62. The

graph of his mental growth is very similar to the normal average. The lower line in Fig. 1 graphically represents the mental growth of a low mentality. This boy is from the group diagnosed as hereditary feeble-mindedness. This group comprises at least two-thirds of all the feeble-mindedness in every community and is not an endocrine problem. The graph however, demonstrates the tendency to a gradual



increasing intelligence with the usual rise at puberty, even though very subnormal.

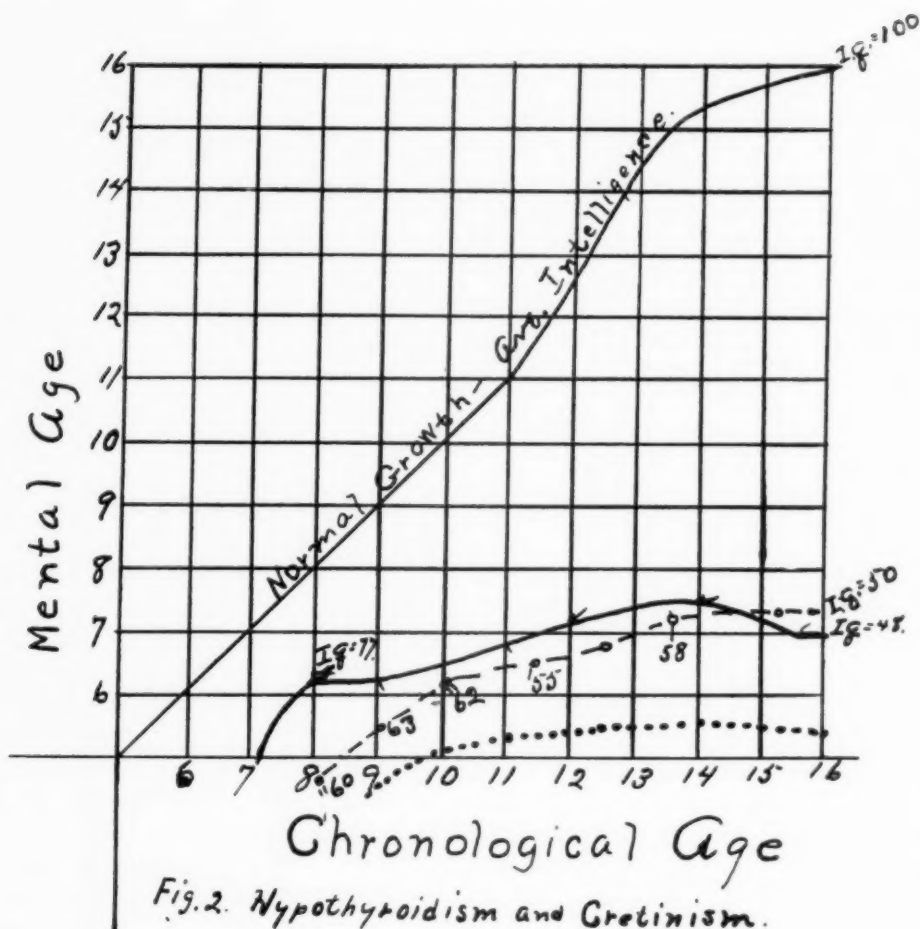
The psychologists of our special schools have for several years been studying a group of children whose intelligence quotient keeps falling. In most of these the gradual fall from year to year can mean but one thing: i.e., the mental age has reached its height while the chronological age goes on, and consequently, a decreasing I.Q. Among the glandular study cases, we found 117 had shown a persistent decrease in intelligence and further, when our cases had been classified according to diagnosis into thyroid and pituitary groups, we found that ninety-three, or eighty percent of those with falling intelligence were in the congenital goiter group. The other (twenty-four) were in the pituitary, anterior lobe deficiency class. On re-study of the twenty-four cases found in the pituitary group, we were impressed by the possibility of a maternal hypothyroidism being the underlying factor in each of these cases; yet at present the pituitary deficiency predominates.

It is a well established fact that cretins are predestined to a fixed low mental age, beyond which they can not go. If untreated, they seldom go above a mental age of six years. Those recognized in infancy or early childhood and treated adequately, appear to gain rapidly for a few months or a year, then go along at the same mental age, approximately eight years, instead of six as the untreated cretins show. With their mental age fixed, their I.Q. naturally goes down. There are eight cretins in this study, three of whom have been treated adequately since infancy.

Their mental growth is shown graphically in Fig. 2 (broken line). The mental growth of the five untreated cretins is shown in the dotted line of Fig. 2. The mental limit of the untreated is just a little under six years, while the three who were given thyroid extract from infancy have been raised to approximately eight years. Their graphs are strikingly similar, reaching their maximum comparatively early, and holding the same mental age thereafter. The usual rise at puberty is not seen.

We have learned nothing new about cretinism. We mention this small group only to re-establish in your mind the type of mental growth that they invariably show: the pre-destined maximal mental age of a child of six or eight, beyond which they cannot rise. Also to state in detail, what Paracelsus pointed out four hundred years ago: that this fixed low mentality is the result of a severe maternal hypothyroidism during the second and third months of foetal life. The whole physical development is limited because the vascular system has been irreparably damaged by the stultifying effect of the maternal hypothyroidism, indirectly due to endemic goiter.

Of the 205 cases of congenital hypothyroidism whose repeated mental tests indicate their mental growth, ninety-three or forty-five percent show a falling intelligence quotient or a fixed mental age. The graphic representation of the mental growth of these ninety-three practically duplicates the mental growth of the cretins. Yet, they are not cretins physically, but certainly they have suffered the same lack of develop-



ment of the cortical areas and the mental growth is thereby limited.

The mental growth curves of all of this group are practically identical. The one shown (heavy line, Fig. 2), is of a girl of sixteen, with intelligence tests each year since the age of eight. She is typical of this congenital hypothyroidism group since her family history immediately rules out hereditary feeble-mindedness. Her mother gave a clear cut history of marked hypothyroidism during the first half of her pregnancy. The girl has a definite congenital goiter

with a persistent thyreo-glossal stalk. Also, an incomplete development of her first molars. At the age of eight and one-half years her I.Q. was 77. She showed a slight increase during puberty, but has a decline following this change. At the age of sixteen, her mental age was only seven years and two months, or an I.Q. of 48. In the discussion of this one girl is concentrated our study of 117 children with a falling intelligence quotient—at least 80 percent of all and most probably 100 percent suffer the same mental

defect: and as stated above 45 percent of all cases of congenital hypothyroidism show this same type of mental growth. Studying this group with their cretinoid type of mental growth, we are convinced that the etiology of the mental deficiency is endemic goiter.

Also, of this group of 205, twenty-two or eleven percent show a definite increase in their rate of mental growth. Of these, nine had been diagnosed and given thyroid, since childhood with quite evident results. The others must have developed sufficient thyroid to completely offset any deficiency and thereby bringing out the maximal mental development. From this it would be easy to conclude that all we should do, is to make the diagnosis early and give sufficient thyroid. But, we also saw nine who had been accurately diagnosed in early childhood and given thyroid persistently, yet their I.Q. had gradually decreased. Apparently their mental growth was limited, as the growth curve is the same as the majority of the ninety-three with falling I.Q. (Fig. 2, heavy line). Therefore, it must depend on the lack of development of the cortical areas, or a limitation set on the functional growth of these areas by an abnormal vascular system.

Above, we referred to the development of the teeth as a diagnostic point in the study of congenital hypothyroidism. We have observed many cases where the first permanent molars show an unusual lack of development. Not a condition of decay or irregular formation due to an early gingival irritation, but a lack of development, a very severe hypoplasia limited chiefly to the cusps. The significant fact is that the

first permanent molars are the first of this set to calcify, calcification beginning about the twenty-fifth week of congenital life. This was emphasized strongly in the instance of three colored boys, age eleven to thirteen, all of whom showed congenital goiter with persistent thyreo-glossal stalk; cretinoid type of mentality, yet they were physically well developed. The first molars in each case were as above described. The other teeth showed perfect enamel as is usual in colored boys. I was quite elated over this complete picture of what we were attempting to establish as a fact, so made arrangements with the school dentist to make casts, drawings, x-ray pictures and careful dental study of these three cases. My enthusiasm proved my undoing, for two of the boys could never be found and the third had gone straightway to his dentist and had his peculiar teeth extracted. We were even unable to locate the dentist and therefore have no models to demonstrate this finding. Cretins of course, have notoriously irregular and defective teeth, but these were not cretins and frequently all other teeth were perfect. We feel that the same maternal hypothyroidism that caused the defect in his thyroid gland, could also produce this stultifying effect on his molars, the points of calcification of which, are, just being laid down at the same time that his fetal thyroid is being so disturbed. And further, this same metabolic disturbance effects the neural development then in progress, and most probably the whole vascular system. We offer this observation knowing we have not yet proven the point.

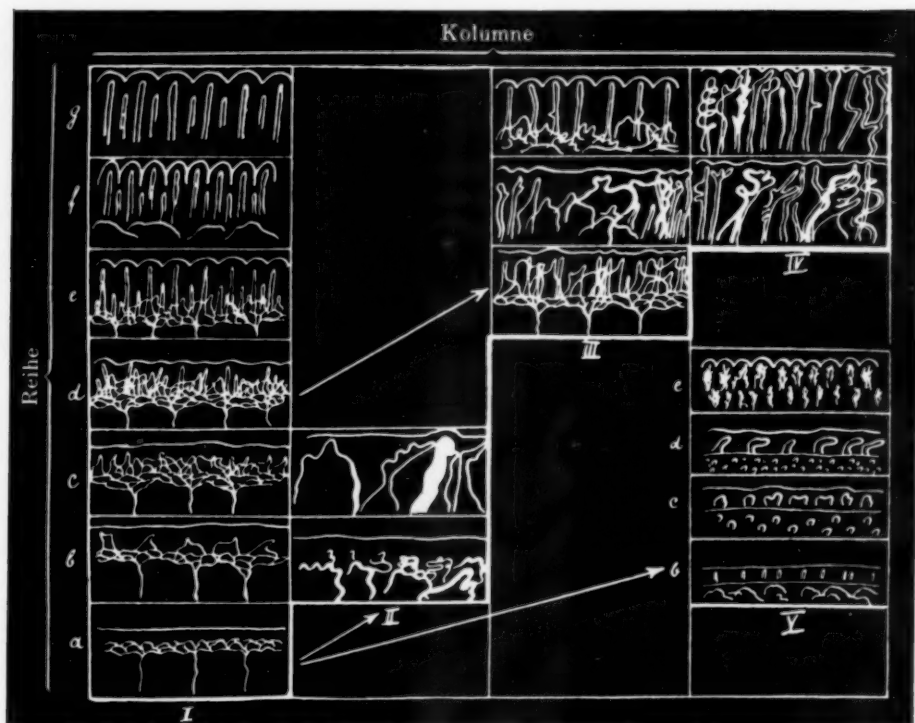


FIG. 3. Development of capillaries of the nail bed in normal children, and in hypothyroid cases.

For the past five years intensive studies have been made of the abnormal development of the circulatory system in cretinism and its allied conditions. The development of the capillaries of the nail bed have been studied and the pattern of development here is considered our closest index to capillary development elsewhere, especially the brain. The structural picture of the capillaries of the nail grooves according to W. Jaensch and W. Wittneber, was placed in a morphogenetic scheme in 1925 by von Hopfner and expanded by him in 1927. This is shown in Fig. 3. Column 1 shows the development in the normal child from birth to one year, by which time the pattern is complete. Column 2 pictures the lack of development which is always seen in

cretins. Columns 3 and 4 show abnormal forms seen in severe hypothyroidism and many cases neuroses and psychopaths due to congenital hypothyroidism. Column 5 are the irregular forms seen most frequently where endemic goiter and cretinism have been more severe. Dr. H. Eggenberger of Hirsau, Switzerland, demonstrates this group in his studies.

These authors have been so impressed by the set picture of capillary development in cretinism and hypothyroidism that they use this as a diagnostic measure for congenital hypothyroidism, where there is no clinical evidence. Last year W. Eisenberg reported his psychological study of 3,100 cases of feeble-mindedness, where this diagnostic measure had been applied to each.



He finds that the teachability of each child runs parallel with the development of his capillaries. He concludes that subnormal mental conditions should always be studied with congenital goiter in mind.

Regardless of the type of study or the diagnostic measures used, we have come to the same conclusion. It emphasizes the fact that in our mildly endemic goiter districts where we have comparatively few cretins, ten percent of all feeble-mindedness is due to endemic goiter. Stated concretely, the city of Detroit has been paying annually \$40,000 more to educate those made defective by this disease, than it would cost to educate the same number of children with normal average mentality. Yet, their education is very limited, which only emphasizes the amount of time, energy and money we have been paying, unknowingly, to this insidious disease. Therefore, it is with considerable pride that we review the Prevention of Goiter as it has been carried out in the state of Michigan for the past six years. The incidence of goiter in the Detroit public schools has been reduced from forty-two percent in 1924 to seven percent in 1929. The

seven percent still present are nearly all congenital goiter. This point is further emphasized by the fact that in 3,185 children studied last year in this endocrine study, we found only ten or one-third of one percent with hyperplastic thyroid enlargements, and too, most of these children were at the age of puberty. It is now an established fact that the endemic goiter problem in Detroit and Michigan has been solved.

For fourteen years we have been studying endemic goiter and its various manifestations through our school population and each year we appreciate more fully the profound wisdom in the statement of my teacher and co-worker, David Marine, "In the Prevention of Endemic Goiter, we are doing vastly more than Retaining the Normal Curve of the Neck."

We wish to state here that this entire study was made possible by the foresight and assistance of the Research Committee of the Detroit Board of Education. Also we wish to express our appreciation to the Dept. of Special Education and the Psychological Clinic for their assistance and co-operation.

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## The Pituitary Factor in Arteriosclerosis\* Its Experimental Production in Rabbits

By ROBERT C. MOEHLIG, M.D. and EUGENE A. OSIUS, M.D., *Detroit, Michigan*

**E**XPERIMENTAL production of arteriosclerosis in rabbits has been accomplished by several workers. Anitschkow and Chalutow<sup>1</sup>, Bailey<sup>2</sup> and others, have used various sorts of diets high in fats or fat-like substances to produce these changes.

Certain facts led us to approach the problem from a new angle. The relationship between the pituitary gland and fat and carbohydrate metabolism suggested that the pituitary secretion might be concerned in arteriosclerosis.

While the exact pathogenesis of arteriosclerosis is somewhat in doubt, nevertheless the cholesterol infiltration of the blood vessels is definitely established.

The importance of the suprarenal cortex in cholesterol metabolism is well recognized. Goldzieher<sup>3</sup> says "The intimate correlation between lipid metabolism, adrenal cortex, and atherosclerosis is striking, although its mechanism is far from being clear. The cholesterol disturbance in atherosclerosis and its relationship to the changes of the adrenals has closed the ring of evidence which seems to prove that adrenal hyperfunction is among the most im-

portant factors in atherosclerosis, which we believe is but one particular manifestation of genuine hypertension."

A correlation between the pituitary and suprarenal glands is, therefore desirable. The pathological changes consisting of hyperplasia of the suprarenal cortex with lipoid storage, so frequently found in arteriosclerosis, hypertension and nephritis becomes an important link in the arteriosclerotic chain.

In several previous papers, one of us (R. C. M.)<sup>4</sup> has emphasized the fact that the state of the pituitary gland was reflected or mirrored in the suprarenal cortex. The relationship between the two organs is well established and there are many pathological conditions which illustrate it. Aplastic states of the pituitary have a concomitant aplasia of the suprarenal cortex and conversely hyperplasia of the pituitary results in hyperplasia of the suprarenal cortex.

We were led to use posterior lobe extract by the work of Krogh<sup>5</sup>. He concluded from his experiments that the posterior lobe secretes a substance in low concentration which maintains capillary tone. Its pharmacologic pressor effect on the (mesodermal) blood vessels is well known and was further

\*This work was carried out with the assistance of the technical staff of Harper Hospital laboratory.

argument for using this substance in the experiments.

Rabbits were divided into four groups as follows:

*Control Group:* Five normal rabbits on a normal laboratory diet consisting of hay, lettuce, vegetables, etc.

*Group A:* This group consisted of 5 rabbits who were fed on a normal laboratory diet plus the addition daily of 12 cc. of cotton seed oil and 4 gms. of anhydrous lanolin for each rabbit. This is the diet used by Shapiro<sup>6</sup> and contains a large amount of cholesterol.

*Group B:* This group consisted of ten rabbits who were placed on the same high fat diet as Group A and in addition received 1 cc. of obstetrical posterior lobe extract (Parke-Davis & Co. Commercial Pituitrin)\* injected either subcutaneously or intraperitoneally.

*Group C:* This group consisting of ten rabbits were placed on a normal laboratory diet the same as the control group and in addition received daily 1 cc. of posterior lobe extract injected subcutaneously or intraperitoneally.

Blood cholesterol estimations (Sackett's<sup>7</sup> modification of Bloor's method) and the weights of the animals were taken every ten days. The lanolin and cotton seed oil were heated and then poured onto the food. All animals were kept under the same conditions in the laboratory.

Except for a few areas of local irritation the animals tolerated the injections of the posterior lobe extract very well.

The first week we gave the injections twice a day and following this once a day over a period of one hundred days so that the average amount injected was 107 cc. of posterior lobe extract.

The effect of the posterior lobe extract injections was interesting. Shortly after each injection the animal became quiet, the peripheral vessels contracted and frequently urine was voided and there were bowel movements. The fur of the animals on the high fat diet as well as those on the high fat diet and posterior lobe injections became and remained more ruffled and shaggy, the appearance of the animal's coats bearing a strong resemblance to that of the guinea pig during acute anaphylactic shock. (Fig. 1.)

From this one may conclude that the high fat diet alone may have some influence upon the fur as already reported by Iscovesco<sup>8</sup>. He injected suprarenal cortex lipoids into rabbits and found that it increased the growth of the fur.

On the hundredth day we began sacrificing the rabbits, by injecting air into the auricular veins. Immediate post-mortem was performed. The organs were weighed and fixed in formalin. The heart and aorta were removed. We shall reserve for a future paper the protocol details and microscopical findings.

We submit a composite curve of the cholesterol estimations of each group, Charts 1, 2, 3, 4.

Because of their importance in the problem of arteriosclerosis and cholesterol metabolism, as previously empha-

\*The pituitrin used in the experiments was kindly supplied us by the Biological Department of Parke Davis & Co. It was conveniently put up for us in specially prepared 30 cc. vials.

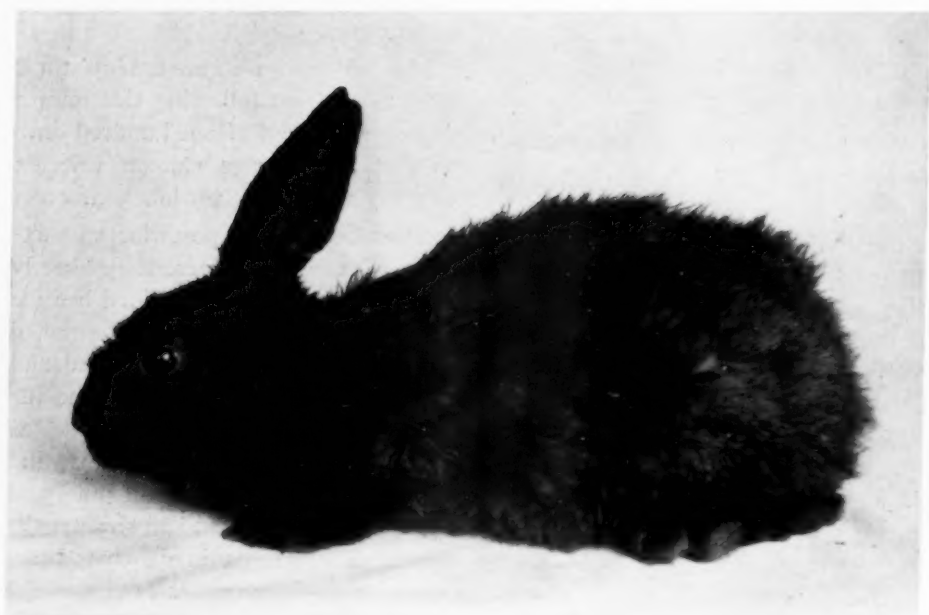


FIG. 1. Rabbit on high fat diet showing fur changes.

sized, we will give the average weights of the suprarenals.

#### AVERAGE SUPRARENAL WEIGHTS

Control Group (Normal diet) . . . .	278 mgms.
Group C (Normal diet plus posterior lobe injections) . . . . .	415 mgms.
Group A (High fat diet only) . . . .	435 mgms.
Group B (High fat diet plus posterior lobe injections) . . . . .	639 mgms.

The suprarenal weight correlated with the body weight (combined weight of adrenals divided by body weight multiplied by 100,000) gave the following suprarenal indexes:

#### SUPRARENAL WEIGHT— BODY WEIGHT INDEXES

Control Group . . . . .	Average index	22.948
Group C (Normal diet plus injections) . . . .	" "	37.52
Group A (High fat diet) . . . . .	" "	38.52
Group B (High fat diet plus injections) . . . .	" "	54.845

It is immediately evident when these suprarenal weights are studied that those receiving the posterior lobe injections have a much higher average suprarenal weight than the non-injected groups. Likewise this is apparent in the average suprarenal indexes.

Under the conditions of the experiment it is apparent that posterior lobe injections increase the size of the suprarenals.

Group C, on a normal diet plus the injections of the extract had an average increase over the control of 137 mgms.

Group B, on a high fat diet plus the injections of the extract had an average increase of 204 mgms. over the group on high fat diet alone and 361 mgms. average increase over the controls. The increase was much higher than the average weight of the controls. The dif-

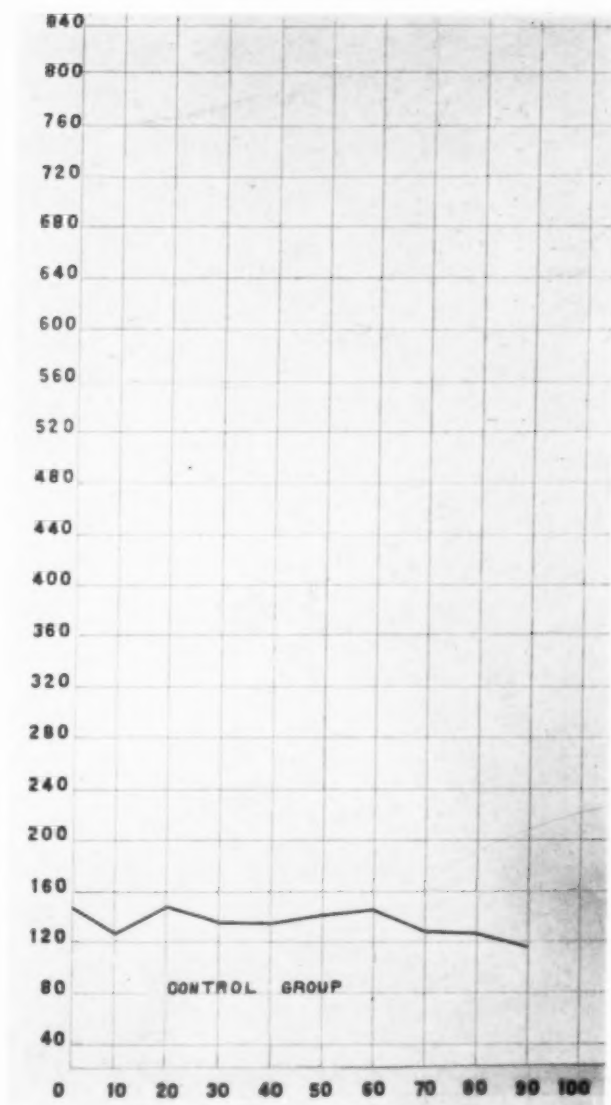


CHART I. Horizontal figures represent days. Vertical figures represent blood cholesterol in mgms.

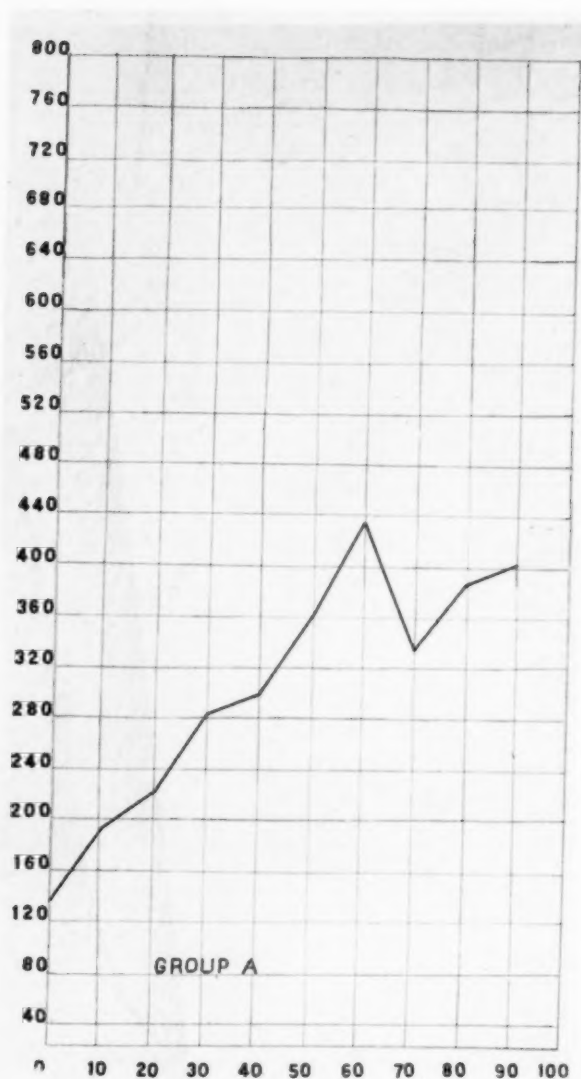


CHART 2. Horizontal figures represent days. Vertical figures represent blood cholesterol in mgms.



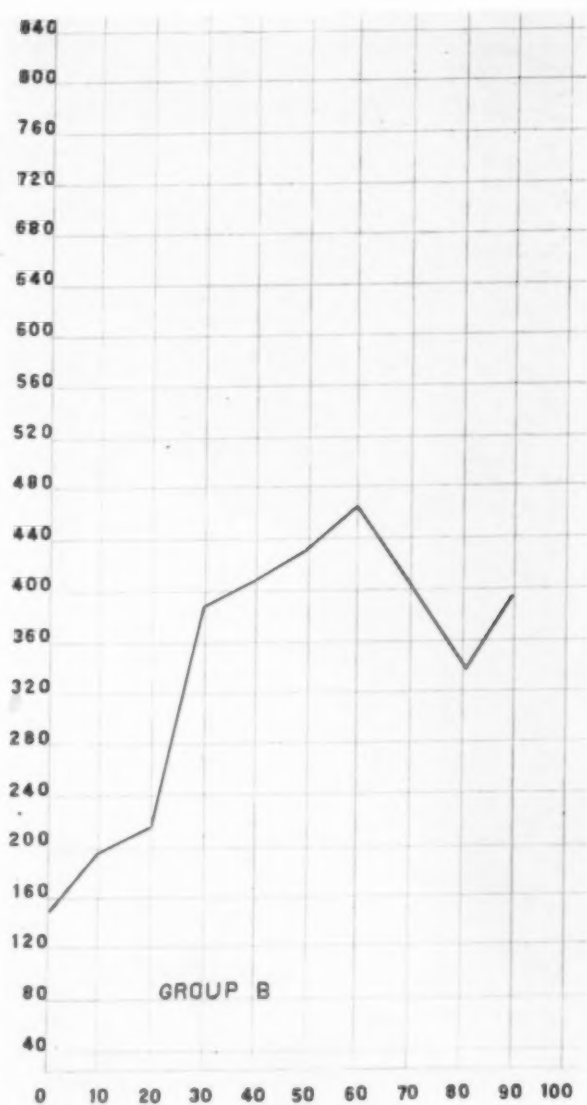


CHART 3 and CHART 4. Same as Figure 1 and Figure 2.

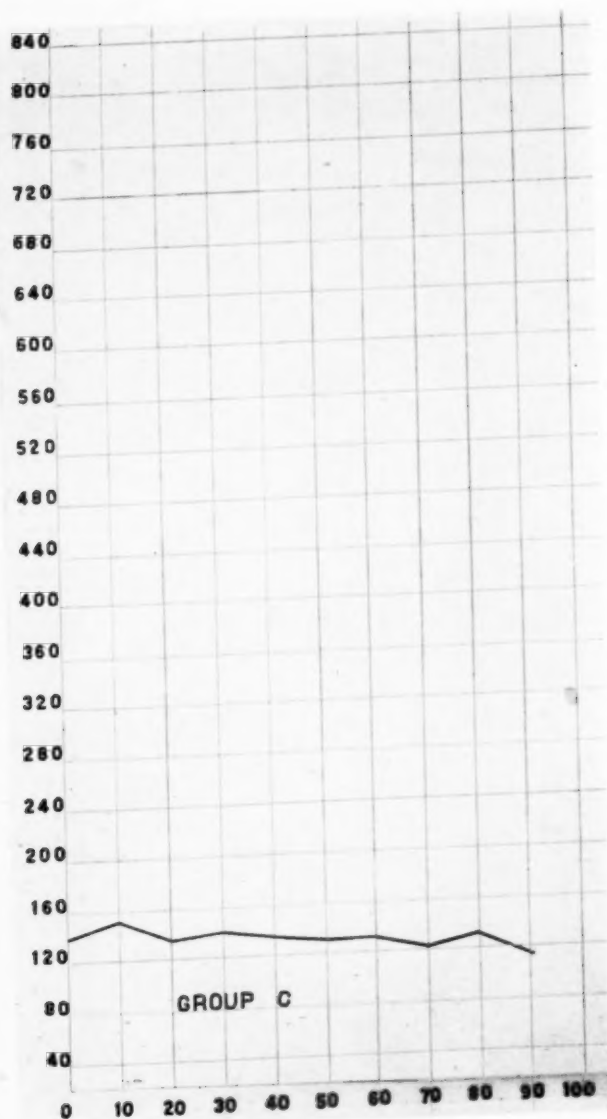


CHART IV.

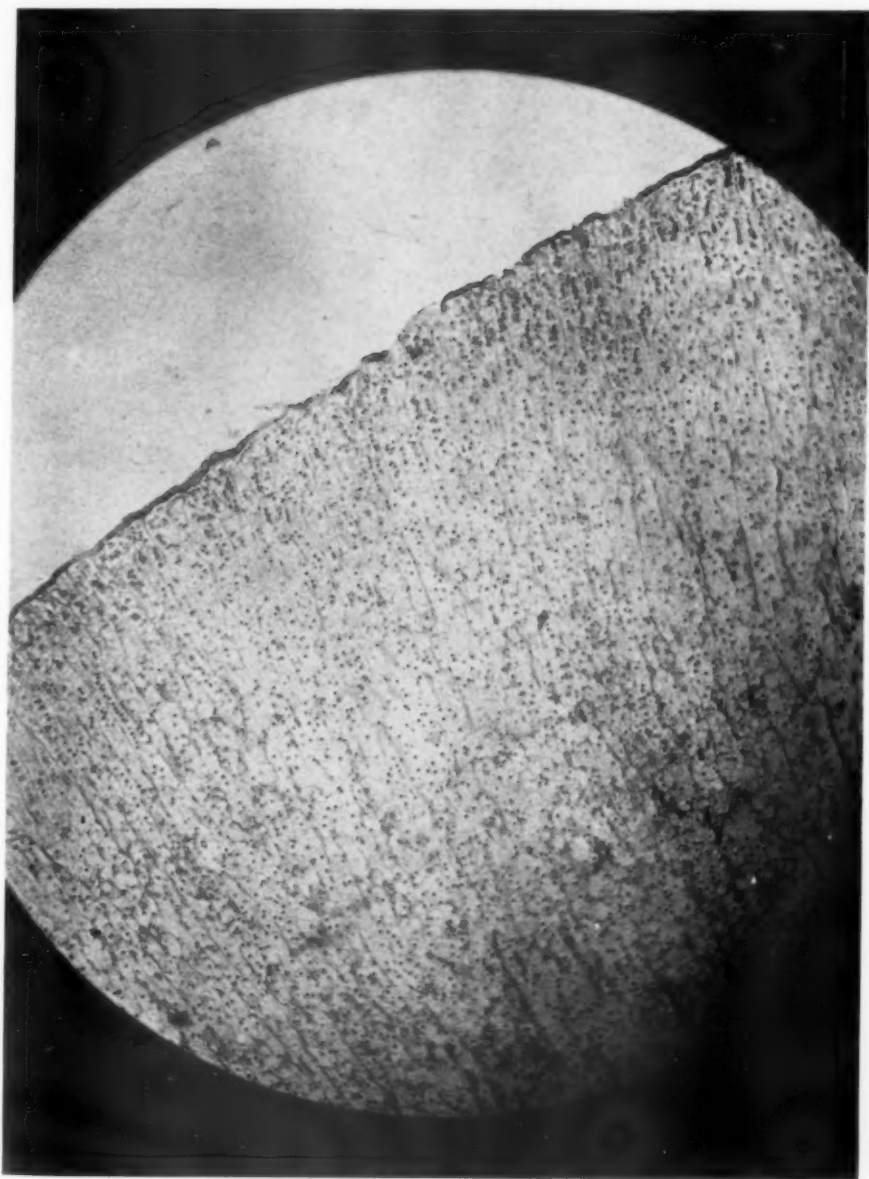


FIG. 2. Adrenal cortex of rabbit on high fat diet plus posterior lobe injections. Note enlargement of glomerular zone, lipoidosis and "exhaustion" appearance.

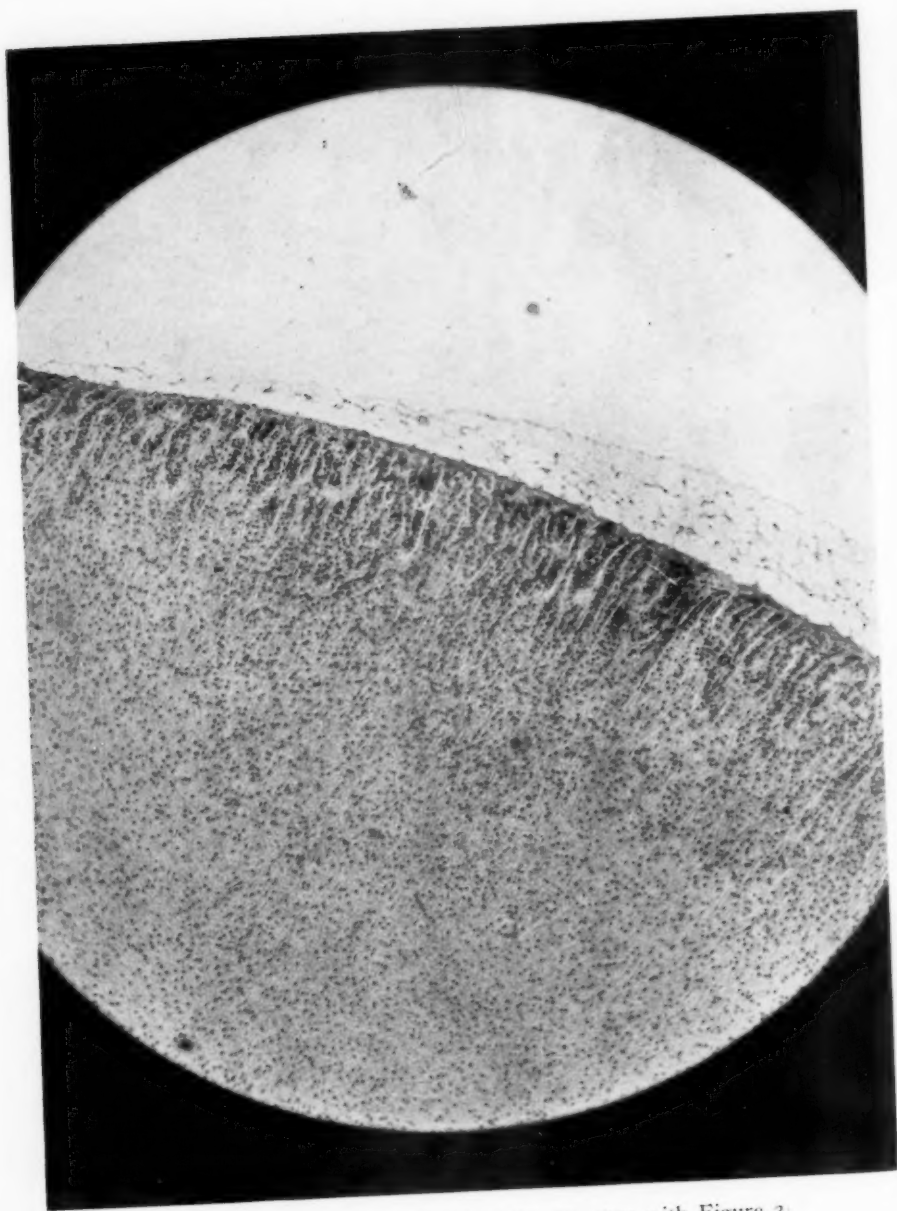


FIG. 3. Normal rabbit adrenal cortex, compare with Figure 2.

ference in suprarenal indexes of the groups is also significant.

Group C receiving the injections alone had an average suprarenal index increase over the controls of 15.57 plus, whereas Group B on high fat and injections of the extract had an average suprarenal index increase over Group A on high fat diet only of 16.32 plus.

The microscopic examination revealed that the increase of the suprarenals was confined to the cortex. No changes were noted in the medulla. (Fig. #II and III.)

#### STUDIES OF THE AORTA

Studies of the aortae revealed the following:

*Control Group:* Not one of the control group showed the least suggestion of arteriosclerosis. (Fig. #IV.)

*Group A: (High Fat Diet.)* Four of the five aortas showed macroscopic arteriosclerotic changes. Illustrative of this is the following as reported by the pathologist, Dr. Plinn F. Morse.

"Aorta shows a few pin point whitish plaques and is scattered over with irregular shaped areas of whitish density producing a somewhat mottled appearance. There is some increase of fat beneath the intima at the exits of the vessels." (Fig. V.)

It is evident that the high fat diet alone produced arteriosclerosis, thus verifying the work of others.



FIG. 4. Aorta of control group.

*Group B:* This group on a high fat diet plus injections of posterior lobe extract showed the most intense lesions of all. Eight of the ten surviving animals showed arteriosclerosis.

The following report by the pathologist illustrates the intensity of the lesions. "Extensive linear and nodular atheroma distributed densely throughout the course of the aorta. Plaques varying in size from several mm. to pin-point around the intercostal arteries." (Fig. VI.)

We do not wish to give the impression that every one of this group was as extensive as reported above, but un-

questionably this group showed the most extensive lesions. We submit photomicrographs of the aorta and coronary vessel (Figs. VII and VIII), rabbit #57 of this group.

*Group C:* This group on a normal diet and posterior lobe extract injections showed the following results.

Six of the ten aortas were reported as macroscopically normal. Four showed changes suggestive of early arteriosclerosis. These changes were not comparable to Group A on high fat diet alone.

Illustrative of the changes noted is the following report of the pathologist:



FIG. 5

FIG. 5. Group A, Aorta, high fat diet only.



FIG. 6

FIG. 6. High fat diet plus posterior lobe extract. Aorta Group B.



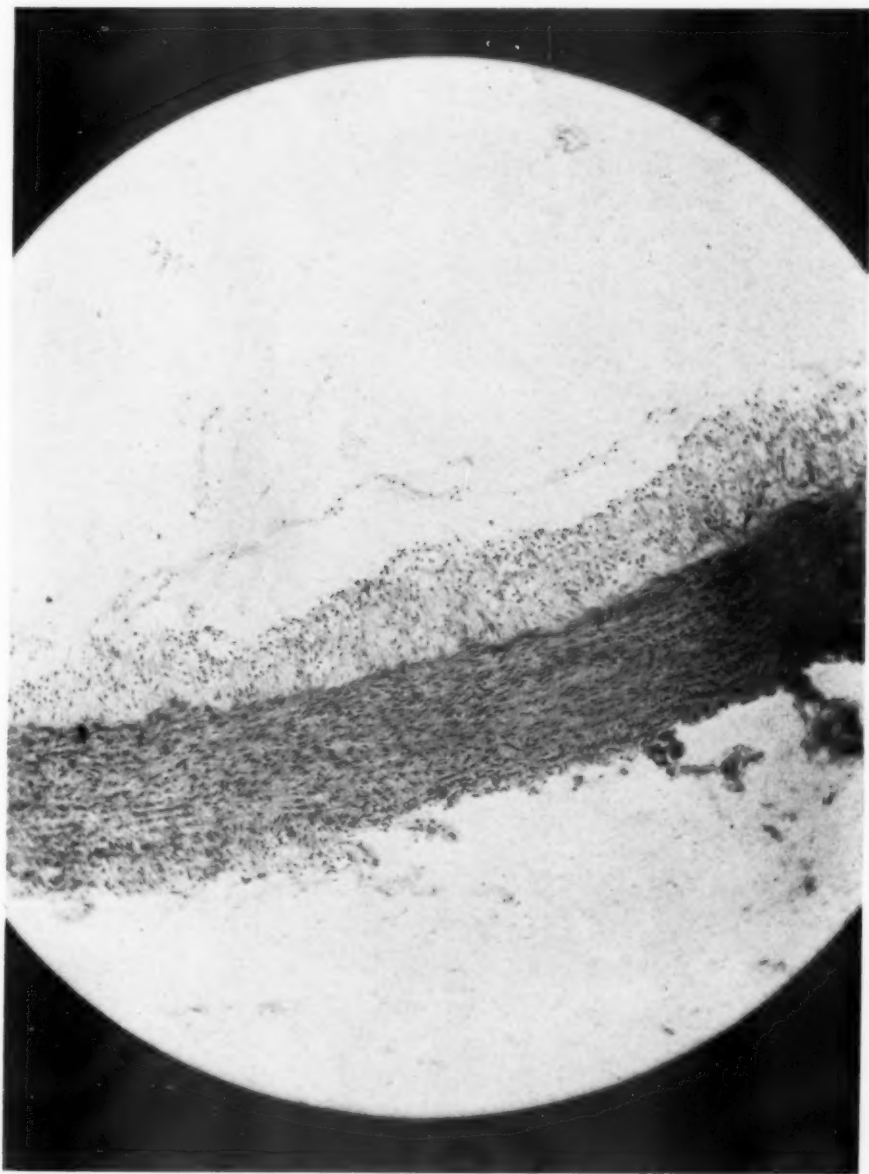


FIG. 7. Extensive lipoidosis of Aortic Intima; rabbit aorta—high fat diet plus posterior lobe injections.

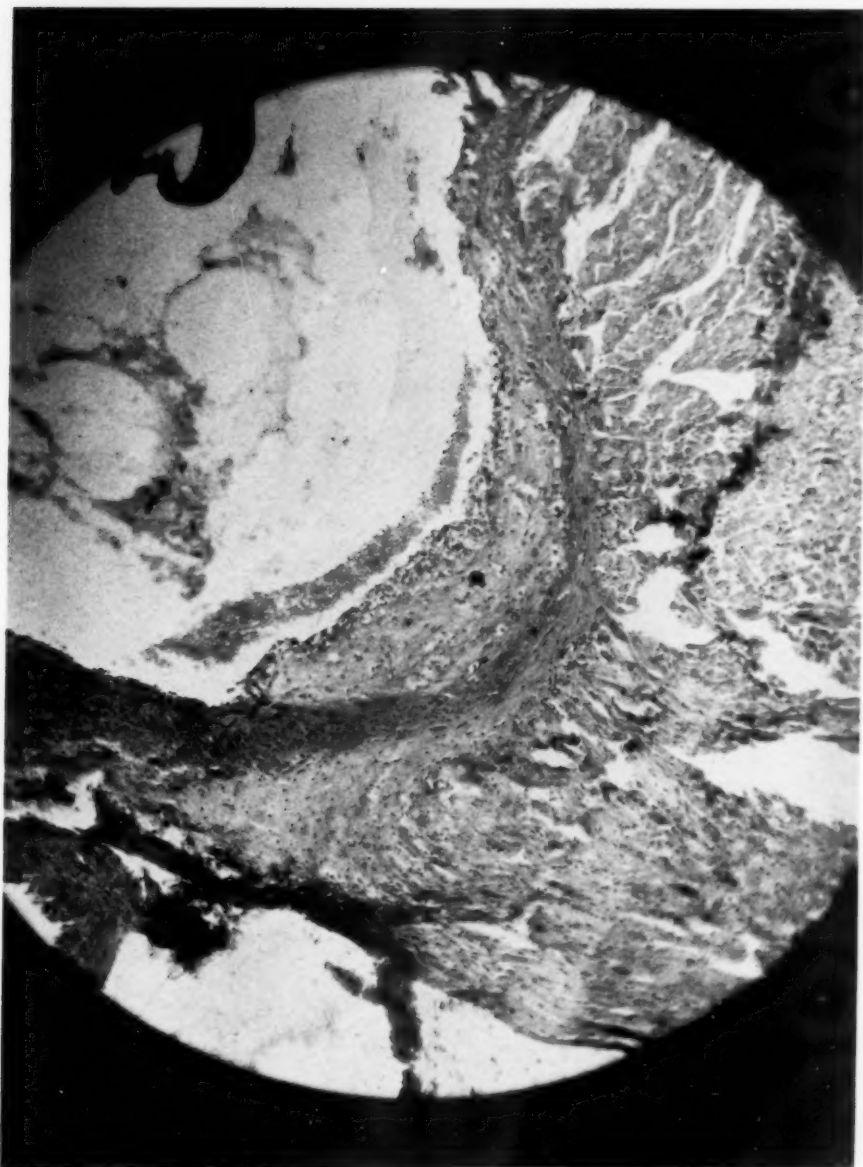


FIG. 8. Extensive arteriosclerosis. Coronary artery of rabbit, high fat diet plus posterior lobe injections.

"Essentially a normal vessel except for diffuse indistinct whitish areas at the cephalic end." (Fig. IX.)

The average suprarenal weight of this Group C was almost as much as the high fat group, being only 20 mgms. less than the latter. The average suprarenal index of Group C was only 1 less than the average of the high fat group.

#### CONCLUSIONS

The importance of suprarenal cortex hypertrophy in arteriosclerosis, hyper-

tension and nephritis makes the suprarenal cortex hypertrophy found in our injected animals of great significance. By the injection of posterior lobe extract alone, without the influence of diet, we are able to produce a suprarenal cortex hypertrophy, an important link in the chain of arteriosclerosis.

Marked production of atheromatous plaques in the rabbit's aorta may be produced within one hundred days by feeding a diet high in cholesterol and the daily injection of posterior lobe pituitary extract.



FIG. 9. Group C. Normal diet plus posterior lobe extract.

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## Lower Fat Diet in Diabetes

By JOSEPH H. BARACH, M.D., *Pittsburgh, Pa.*

**T**HERE are today three distinct views concerning the proper diet in diabetes. One group of workers believes that carbohydrates should be kept at a point believed to represent glucose tolerance of the patient. The second group advocates a high fat, non-ketogenic low carbohydrate diet. The third group, holding the most recent views, advocates what seems like a very high carbohydrate and low fat diet. All agree upon the desirability of avoiding ketosis, meeting caloric needs and supplying the patient with a physiologic diet. It is readily seen that each of these concepts of what constitutes a physiologic diet for the diabetic, differs markedly. Those who give little carbohydrate, believe it advantageous to give small doses of insulin, and the fewer doses per day, the better. Those who allow a high carbohydrate diet are not deterred by the necessarily large doses of insulin. Each of these views is based on presumably good reasons, and satisfactory end results are claimed for the three methods. As the problem stands today, authorities are not in agreement and it is left with the average practitioner to decide for himself as to which is the method of choice. And yet, because of his lesser experience, it is this practitioner who is least qualified to make the decision. This is not a healthy state of affairs; and a unified effort

should be made toward standardization of a treatment for this disease.

### CRITERIA IN TREATMENT

At this point I wish to reiterate certain generally accepted facts, which must be recognized if one is to treat diabetes intelligently and successfully. As far as is known today, these should be considered as actual laws governing treatment of this disease.

1. Caloric requirement for adults ordinarily 30 to 35 calories per kilo body weight daily.
2. Protein requirement for adults never less than .66 gram and ordinarily 1.0 gm per kilo body weight daily.
3. Blood sugar not to exceed 125 mgm per 100 cc. Avoid glycosuria.
4. Sufficient carbohydrate with or without insulin to prevent ketosis.
5. Fat carbohydrate ratio: Experience shows that when ratio of fat to carbohydrate exceeds 3 to 1, ketosis will develop. When physiologic proportions of carbohydrate, protein and fat are oxidized, ketosis does not occur.
6. Insulin affects and is affected by carbohydrate, protein and fat in the diet; insulin affects the total metabolism.

7. Total caloric value of diet and nutritional state, the body weight of patient, should constantly be kept in mind.
8. The patient should be brought toward normal or slightly below normal weight.
9. Where there is acetone and diacetic acid without glycosuria, carbohydrate utilization is too low.
10. Where there is acetone and diacetic acid with glycosuria, a reduction in fat, protein or carbohydrate or administration of sufficient insulin is imperative.

#### THE NORMAL DIET

Experience has shown that a diet in which 67% of the calories are obtained from carbohydrate, 16% from protein and 17% of the calories from fat is physiologically adequate in health and in disease. In the light of what we have learned from diabetic and other nutritional studies, we know that an individual doing light work will maintain good health at 30 to 35 calories per kilo. Thirty calories per kilo is generally satisfactory for the average diabetic. It may be that the usual American diet is higher in fat than that of the Euro-

pean, because fat is more plentiful here, the reason being economic rather than a special craving or physiologic need for a high fat ration. There are evidences in health and disease which point to the fact that a low rather than a high fat diet is preferable. Believing this to be so, we assume that the same principle should guide our effort of returning the diabetic to a state of comparative health.

#### APPROACH TO TREATMENT OF THE DIABETIC

When a patient first comes to us we are confronted with the question as to whether the severity of the disease is a useful guide to treatment or whether we should ignore the actual state of the diabetes and attempt to return the patient to a nearly normal diet as quickly as possible. In practice, this amounts to giving a low carbohydrate and high fat diet, or a high carbohydrate and low fat diet with insulin.

#### VARIATIONS IN PRACTICE

The following table illustrates wide variations in the diet prescription. The figures indicate the diet ordered at the

TABLE I.

	Carb.	Protein	Fat	Calories
Newburgh and Marsh (Entering Hosp.)	27.0 gm	35 gm	170 gm	1778
Graham " "	28	40.6	175	1840
Wilder " "	33	46	192	2044
Campbell " "	40	47	146	1662
Allen " "	45	70	182	2098
Rabinowitz " "	50	50	150	1750
Bartlett " "	50	70	180	2100
Baehr " "	60	48	138	1674
Harrop " "	70	70	171	2099
Kellpgg " "	75	46	177	1714
Foster " "	107	70	154	2094
Joslin (When Leaving Hospital)	109	84	135	1995
Barach (Entering Hospital)	116	70	150	2100
Sansum " "	228	65	114	2198 Insulin
Geyelin (Children)	2 to 4 gm	1.0	1.0	per kilo



beginning of treatment, for a patient of 70 kilos.

From these figures it will be seen that approach to the diabetic problem is highly variable. The carbohydrate ration for the patient of 70 kilos varies from 27 to 288 gm. I know that these values no longer hold good for the present day practice of some of the authors quoted, and that larger carbohydrate rations are now being given.

Low carbohydrate, means likewise a high fat diet. Objections to the high fat diet are many. While there is not as yet an abundance of proof for histologic tissue change brought about by excessive fat in the diet, it is true that such evidence is notably increasing.

On the other hand, there is no question at all concerning the constantly menacing chemical disturbances which follow in the wake of the high fat diet.

Clinically, there is plenty of evidence of disturbances associated with high fat diet in diabetes. Sudden change in character of the food, large amounts of fat, coarse vegetables, roughage and bran are all part of the diet when small amounts of carbohydrate are taken. In my experience, the high fat diet is at times accompanied by epigastric distress, at times real pain. Some patients develop pylorospasm, others have been wrongly diagnosed gall bladder colic and some have attacks of colitis. I have seen these various symptoms disappear completely within a few days, after instituting higher carbohydrate diet. In some there is anorexia, nausea and diarrhea; all of which are discomforting and harmful. With high fat, achylia and diarrhea are not uncommon sequelae. It is also well to think of

mineral deficiencies in a diet too low in carbohydrate foods.

#### CARBOHYDRATE TOLERANCE OF THE PATIENT WITH AND WITHOUT INSULIN

Theoretically, the carbohydrate tolerance of a patient can be estimated by making a few rapid calculations. It is true that this calculation may represent the carbohydrate content of the patient's diet, but the results of this calculation, minus glucose output does not necessarily represent the actual tolerance of the patient for carbohydrates. The total caloric value of the diet as compared with the patient's requirement for that day, and the amount of protein and fat in the diet, are important factors in determining actual tolerance. Likewise the estimated carbohydrate tolerance of a patient when he first becomes sugar free and the estimated tolerance after he has been sugar free for a month, will frequently not be the same at all. This we have known for a long time.

Apparent improvement during the early treatment of a patient does not necessarily indicate renewed pancreatic function or, as some would have us believe, a regeneration in the islands of Langerhans. For such reasons, I believe that reported gains in carbohydrate tolerance frequently are not as real as they seem. To be certain of an increase in carbohydrate tolerance of a patient under laboratory control, one must take cognizance of the patient's weight, the activity of the patient, the total caloric intake and the relative proportions of carbohydrate, protein and fat in the diet. If these conditions are kept nearly constant, and maintained for a suffi-

cient length of time, then the difference between glucose intake and output, will have truer significance.

#### BODY WEIGHT

This can be successfully controlled in most cases. A group of 142 cases reveals the fact that at beginning treatment 62 were above ideal weight, 78 were below weight and 2 cases were of correct weight. As treatment progressed, 80% of the overweight showed a loss in the direction of the ideal weight, but 20% showed a gain in weight regardless of our effort in that direction. Of the underweight cases 90% were made to gain and 10% showed loss up to the time of these calculations. On the whole, weight control is in the hands of the doctor and presents no difficulties if the patient will co-operate.

#### WHEN DOES THE POTENTIAL DIABETIC BECOME DIABETIC?

In 1924 after a study of 375 diabetics, I found that on the basis of 30 calories per kilo, allowing that the normal diet obtained approximately 67% of its calories from carbohydrate, 16% from protein and 17% from fat; only one diabetic in a hundred could take more than half the normal carbohydrate ration. A similar calculation in a group of 97 cases at the present time, shows that 92 out of 97 diabetics had a carbohydrate tolerance of less than 50% of the normal. Eighty-six percent of this group had already lost two-thirds of the normal tolerance when they came for treatment. In another group I find that 130 out of 138 diabetics had a carbohydrate tolerance of less than 150 gram carbohydrate. It is

apparent that most diabetics tolerate less than 150 gram carbohydrate, and only exceptional cases still possess one-half normal tolerance. The majority (86%) of diabetics are down to one-third normal carbohydrate tolerance when they come for treatment. This brings us to the realization that when an individual has lost two-thirds of the normal carbohydrate and other food tolerance, his disease becomes manifest and the patient seeks medical aid.

#### APPROACH TO TREATMENT

Under these conditions, which is the course to follow? As already stated, high fat diet offers definite disadvantages both theoretically and practically. High protein diet, higher than 1 gram per kilo for adults is likewise unnecessary. I believe that the majority of healthy city people engaged in ordinary occupations take no more than 1 gram per kilo body weight. I am certain that women take less than 1 gram protein per kilo, daily.

#### THE CARBOHYDRATE RATION

This brings us to consideration of the carbohydrates. The important question being, whether we will do well to keep to a low carbohydrate ration which is the common practice today, or whether we will obtain ultimately better results by approaching the normal amount. During the past six years I have kept my patients near the one-third normal carbohydrate when possible and I made effort to avoid insulin. Surveying one group of 100 cases thus treated, I find that there was no change in tolerance in 47, and there was a loss of tolerance in 36 cases and that 17 showed a gain in carbohydrate toler-

ance. By a gain in carbohydrate tolerance for this group, I mean the same protein, fat and insulin dosage and greater carbohydrate intake, without glycosuria and hyperglycemia. This is not a particularly impressive result. The best that can be claimed for it is that these individuals have lived and worked in comfort, and on the whole are going along very satisfactorily. Body weight has been controlled in the ideal direction and normal growth has taken place in the young. The arteriosclerotic and hypertensive diabetics seem no better or worse than hypertensive non-diabetic patients.

#### HIGH VERSUS LOW CARBOHYDRATE DIET

Geyelin was one of the very first to advocate the high carbohydrate diet. Sansum's work is well known. While my practice has been to allow one-third ( $5/15$ ) normal carbohydrate, one gram protein and fat q. s. for thirty calories per kilo, Sansum's allowance amounts to three-fifths ( $9/15$ ) of the normal carbohydrate, 0.66 to 1.0 gram protein and fat q. s. for total caloric requirement.

In a group of one hundred and fifty patients, I find that fifty-eight are taking insulin; the average dose per patient is 21.3 units daily. Sansum reports an average dose of 42 units daily. Considering that my diet contains  $5/15$  and Sansum's diet contains  $9/15$  of the normal carbohydrate it is readily seen why Sansum's patients require twice as much insulin. A question of importance is whether on the higher carbohydrate diet, the patient is sufficiently safe against accidents from unexpected hypoglycemia following the use of

large doses of insulin; whether blood sugar can be maintained at a satisfactory level, whether patients will be living more normally, withstanding the wear and tear of life better, and whether they will suffer less deterioration or more, as the years go on. These questions have not yet been answered in the affirmative to the satisfaction of all; but it is likewise true that after a larger experience with relatively high carbohydrate diets we may come to the conclusion that it is the better treatment.

As shown in Table 1, the diet on which my patient is placed when entering the hospital is higher in carbohydrate than is usually allowed, except by Geyelin for children and Sansum for adults. The diet that I have been using (one third normal) contains about half of the carbohydrate allowed by Sansum, for a patient of similar body weight.

#### EXCHANGING FAT FOR CARBOHYDRATE

I have chosen for the present study a group of fifty diabetics of nearly all ages, whose diet is being changed to a higher carbohydrate ration. Each week the patient adds five or ten gram carbohydrate and subtracts its caloric equivalent in fat. We continue this exchange so long as the patients get along with their former dose of insulin and without hyperglycemia or glycosuria. The protein is continued at 1 gm. per kilo; so that this modification represents a replacement of fat by carbohydrate.

Up to the present writing, I find that in one to three months, I have been able to increase the carbohydrate in amounts varying from ten to seventy-five gm.,

the average increase being 42 gram, all of which indicates that previously estimated carbohydrate tolerance was too low. Some have had the large carbohydrate ration for a short time only and have not yet reached their full capacity for this exchange. Twenty percent of the cases found it necessary on their own initiative to temporarily increase the insulin dosage seven units per day. In a number of these, increase was coincidental with acute colds. Sixteen percent reduced their insulin 4 units per day. In two cases insulin was entirely eliminated. The others required no change of insulin. Seven patients lost a total of eleven pounds, the equivalent of 1.4 pounds each; twelve gained a total of forty-five pounds, the equivalent of 3.7 pounds each. I am satisfied that these patients are better off for the change in diet; they feel better and as far as I can see, they are better in every way.

#### THE REFRACTORY DIABETIC

There is a group of diabetics which have in the past been difficult to treat because of their inconstant response to diet and insulin. On the same diet and insulin dosage these patients were sugar free one day and had a high glycosuria and hyperglycemia the following day. At times they were suspected of cheating and at times we felt that such responses could only be due to nervous strain or nervous unbalance, whatever that might be. The fact remained that we could not control them with three and in some cases with four doses of insulin per day. These outstanding cases, some of which had been under my care five or six years, under the newer regime with lower fat diets,

have settled down to being "ordinary" diabetics; instead of being in the throes of hyperglycemia in the morning and hypoglycemia at night, they are now free of such irregularities and are under satisfactory control. I believe that their refractory state was due to the high fat in the diet. It is apparent that with the high fat ration large quantities of insulin was used up in an irregular fashion. For these patients, the low fat diet with its proportionate higher carbohydrate ration has been of great benefit.

#### ORDERING THE DIET: METHOD

By the following procedure I find that we determine the patient's diet more quickly than by subjecting them to a period of undernutrition, followed by a gradual return to maintenance diet. With this procedure, I have never seen any ill effects and the stay in the hospital is shortened. Tables 2 and 3 give the normal weight for children and adults.

TABLE II

NORMAL WEIGHT—6 MONTHS TO 17 YEARS

Height	Age	Weight	
		Male	Fem.
26 in.	6 mos.	18 —	2 lbs.
27 in.	8 mos.	20 —	2 lbs.
28 in.	10 mos.	21 —	2 lbs.
29 in.	1 yr.	22 —	2 lbs.
32 in.	1½ yr.	25 —	2 lbs.
34 in.	2 yr.	27 —	1 lbs.
35 in.	2½ yr.	30 —	2 lbs.
37 in.	3 yr.	32 —	2 lbs.
38 in.	3½ yr.	34 —	2 lbs.
39 in.	4 yr.	36 —	2 lbs.
40 in.	5-7 yr.	38 —	1 lbs.
42 in.	5-8 yr.	42 —	1 lbs.
44 in.	5-8 yr.	46 —	1 lbs.
46 in.	5-9 yr.	50 —	2 lbs.
48 in.	6-11 yr.	54 —	2 lbs.
50 in.	7-12 yr.	58 —	1 lbs.
52 in.	7-12 yr.	62 —	2 lbs.
54 in.	8-13 yr.	70 —	2 lbs.
56 in.	9-14 yr.	78 —	2 lbs.
58 in.	10-16 yr.	86 +	2 lbs.
60 in.	10-17 yr.	96 +	4 lbs.

Female weight, subtract or add number of pounds designated. See Conversion Table.

TABLE III  
NORMAL WEIGHT 17 TO 34 YEARS

Ages	17-19	20-24	25-29	30-34
Height	M-F	M-F	M-F	M-F
4' 10"	109-1	115-4	120-6	123-6
4' 11"	111-1	117-4	122-6	125-6
5' 0"	113-1	119-4	124-6	127-6
5' 1"	115-1	121-4	126-6	129-6
5' 2"	118-1	124-4	128-6	131-6
5' 3"	121-1	127-4	131-5	134-6
5' 4"	124-1	131-5	134-5	137-5
5' 5"	128-2	135-6	138-6	141-5
5' 6"	132-2	139-6	142-6	145-5
5' 7"	136-2	142-5	146-6	149-5
5' 8"	140-2	146-5	150-6	154-6
5' 9"	144-3	150-5	154-6	158-6
5' 10"	148-3	154-5	158-6	163-8
5' 11"	153-3	158-5	163-8	168-10
6' 0"	158-3	163-6	169-10	174-12
6' 1"	163-3	168-6	175-12	180-14

NORMAL WEIGHT 34 TO 54 YEARS

Ages	35-39	40-44	45-49	50-54
Height	M-F	M-F	M-F	M-F
4' 10"	125-5	128-4	130-3	131-2
4' 11"	127-5	130-4	132-3	133-2
5' 0"	129-5	132-4	134-3	135-2
5' 1"	131-5	134-4	136-3	137-2
5' 2"	133-4	136-3	138-2	139-1
5' 3"	136-4	139-3	141-2	142-1
5' 4"	140-4	142-3	144-2	145-1
5' 5"	144-4	146-3	148-2	149-1
5' 6"	148-4	150-3	152-1	153-1
5' 7"	152-4	154-3	156-1	157-0
5' 8"	157-5	159-3	161-2	162-0
5' 9"	162-6	164-5	166-3	167-1
5' 10"	167-8	169-7	171-5	172-2
5' 11"	172-10	175-9	177-7	178-4
6' 0"	178-13	181-12	183-10	184-7
6' 1"	184-16	187-15	190-13	191-10

Female weight, subtract number of pounds designated. See Conversion Table.

Table 4 is a conversion table, pounds to kilos, the use of which reduces calculation for the prescribing physician to a minimum.

Table V gives the normal diet for all ages. It is given here for comparison. We use these values as our guide in the treatment of nutritional disturbances, cardio-vascular disease, essential hypertension, nephritis and in other diseases. This is a safe diet and well within physiologic values.

Table VI indicates gram per kilo diet, for the diabetic.

#### PROCEDURE

1. According to age and height of patient, multiply gm. Carbohydrate, Protein and Fat by the number of kilos

TABLE IV  
CONVERSION TABLE

Body Weight Lbs.	Body Weight Kilo.	Body Weight Lbs.	Body Weight Kilo.	Body Weight Lbs.	Body Weight Kilo.
15.4.....7	83.6.....38	151.8.....69			
17.0.....8	85.8.....39	154.0.....70			
19.8.....9	88.0.....40	156.2.....71			
22.0.....10	90.2.....41	158.4.....72			
24.2.....11	92.4.....42	160.6.....73			
26.4.....12	94.6.....43	162.8.....74			
28.6.....13	96.8.....44	165.0.....75			
30.8.....14	99.0.....45	167.2.....76			
33.0.....15	101.2.....46	169.4.....77			
35.2.....16	103.4.....47	171.6.....78			
37.4.....17	105.6.....48	173.8.....79			
39.6.....18	107.8.....49	176.0.....80			
41.8.....19	110.0.....50	178.2.....81			
44.0.....20	112.2.....51	180.4.....82			
46.2.....21	114.4.....52	182.6.....83			
48.4.....22	116.6.....53	184.8.....84			
50.6.....23	118.8.....54	187.0.....85			
52.8.....24	121.0.....55	189.2.....86			
55.0.....25	123.2.....56	191.4.....87			
57.2.....26	125.4.....57	193.6.....88			
59.4.....27	127.6.....58	195.8.....89			
61.6.....28	129.8.....59	198.0.....90			
63.8.....29	132.0.....60	200.2.....91			
66.0.....30	134.2.....61	202.4.....92			
68.2.....31	136.4.....62	204.6.....93			
70.4.....32	138.6.....63	206.8.....94			
72.6.....33	140.8.....64	209.0.....95			
74.8.....34	143.0.....65	211.2.....96			
77.0.....35	145.2.....66	213.4.....97			
79.2.....36	147.4.....67	215.6.....98			
81.4.....37	149.6.....68	217.8.....99			
		220.0.....100			

2.2 lbs.=1.0 Kilo

TABLE V  
DIET PER KILO BODY WEIGHT IN HEALTH

Age	Gm. Carb.	Gm. Prot.	Gm. Fat	Calories
to 4 yrs.	10.0	3.0	3.10	80
4-10 yr.	10.0	1.5	2.66	70
10-17 yr.	7.5	1.5	2.66	60
17-25 yr.	5.0	1.5	2.10	45
Adult	5.0	1.0	0.66	30

TABLE VI  
DIABETIC DIET PER KILO BODY WEIGHT  
CARBOHYDRATE 1/2 NORMAL

Age	Gm. Carb.	Gm. Prot.	Gm. Fat	Calories
to 4 yrs.	3.3	3.0	3.3	55
4-10 yr.	3.3	1.5	3.4	50
10-17 yr.	2.5	1.5	3.2	45
17-25 yr.	1.67	1.25	2.0	40
Adult	1.67	1.00	2.14	30

which represents the desired body weight for that patient. Table VI is based on one-third normal carbohydrate, 1 gm. protein and sufficient fat to meet caloric needs.

2. When patient is sugar free three days, add 10 gm. carbohydrate and deduct 4.5 gm. fat from total diet. Repeat



this until hyperglycemia or glycosuria appears.

3. If patient cannot take this (1/3 normal diet) without glycosuria, insulin is advisable.

4. If patient shows hyperglycemia or glycosuria, give insulin before breakfast. If that is insufficient, give second daily dose before evening meal. In exceptional cases when necessary, give third daily dose before luncheon. Allow one unit insulin for each 2 gm. glucose output.

5. If patient can take one-third normal diet or more, without hyperglycemia; more carbohydrate and insulin is optional with doctor and patient.

6. After patient has been sugar free for one month, try substituting carbohydrate 10 gm. for fat 4.5 without changing insulin. Continue this exchange toward the normal diet unless hyperglycemia or glycosuria appears.

7. If tolerance is improving, increase of carbohydrate or reduction of insulin is again optional with doctor and patient.

#### SUMMARY

Numerous workers in this field are agreed that high fat diets are undesirable and it is assumed that only the smallest amounts of fat which will meet the caloric needs of the patient should be prescribed. At best, the fat in the diabetic diet always exceeds normal values. Although it has been my practice to allow a generous amount of carbohydrate, I find that by a progressive exchange of fats for carbohydrates, patients seem to take care of considerably more carbohydrate than was formerly allowed. In a comparatively short time this exchange has permitted an increase of 10 to 75 grams carbohydrate per day. This exchange has been welcomed

by the patient in every instance. My experience with this group of fifty patients leads me to believe that the larger carbohydrate ration is an advance in diabetic therapy.

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## Linseed Meal Sensitization\*

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**A**LTHOUGH occasional references to flaxseed or linseed sensitization are scattered through the vast literature on allergy, it seems to me that hypersensitiveness to this substance is deserving of further emphasis.

### REVIEW OF THE LITERATURE

Contact with ground flaxseed; in the preparation of flaxseed poultices, has been known to produce urticaria of the hands and arms, and also asthmatic attacks. Walker<sup>1</sup> reported one case of angioneurotic edema caused by flaxseed.

Cooke<sup>2</sup> referred to one patient with asthma and coryza from linseed, and testing this patient intradermally with linseed extract produced an immediate constitutional reaction manifested by asthma, coryza, urticaria, and also angioneurotic edema of the neck lasting two days. This experience illustrates the danger of testing intradermally with such a potent allergen as linseed, especially when there is a positive or suspicious history of allergic symptoms from inhalation or ingestion of this substance. Cooke also mentioned flaxseed as giving another patient asthma.

Meyer<sup>3</sup> reported the case of a man, complaining of asthma, who two years before consulting him had gone on a farm to raise chickens. Shortly after taking up that work he noted that attacks of shortness of breath accompanied his working about in the dust of straw, alfalfa, or chicken feed. There was complete cessation of symptoms when he was away from the farm. His asthma was more marked in the winter. On the first visit, negative intradermal tests were obtained with feathers, cereals, hay, straw, and cow epithelium. At the request of his physician he had brought with him samples of feeds and powders from the farm, and from these, extract solutions were prepared. On the second visit, he was tested with them, and markedly positive reactions were obtained with two, namely, a poultry powder and a scratch feed. The most marked reaction of all, however, was elicited with an extract of flaxseed. Extracts of house dust, orris, and animal danders gave negative reactions. On the third visit, he reported that among other offending feeds he had gotten rid of one poultry tonic containing 70 per cent flaxseed. Relief was prompt, and when last seen he reported continued general good health, interrupted by only infrequent and mild attacks in cleaning out the

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chicken house. He continued, of course, to avoid flaxseed feeds.

In testing 293 patients having allergic dermatitis, Piness and Miller<sup>4</sup> obtained positive reactions to flaxseed in nine patients, but in only one, a druggist, could they say that this substance was more than a possible contributing cause of the allergic dermatitis.

Nicholson<sup>5</sup> discovered seven cutaneous reactions to flax and linen in testing 158 patients with a series of from 125 to 150 proteins. He stated that these reactions would have been missed with a small series of tests. The cutaneous scratch was used for testing, and the reactions were all very marked. They were equally marked when a small amount of linseed meal, dissolved in a drop of deci-normal sodium hydroxide was rubbed into a scratch. Only one of these seven patients, a farmer, volunteered the information that he was hypersensitive to flax. I will abstract Nicholson's reports of these seven cases.

*Case 1*, was a young man of 28 who had suffered from very severe attacks of asthma since he was 5 years of age. Protein sensitization tests showed the following positive reactions: flaxseed + + + +, chicken feathers + + +, and mild or doubtful reactions to a number of other substances. The offending substances were removed from his diet and surroundings, but the attacks continued with their usual severity. After a month's trial of the above desensitization by injections of a protein extract of flax and chicken feathers was tried. The first dose was 0.1 c.c. of a 1 to 50,000 solution. Little or no reaction occurred, but after the third dose, which was increased according to schedule, a most violent anaphylactic attack occurred. It began with tingling of the ears and extremities. Later there was almost total suffocation, cyanosis, and a drop

in the blood pressure. Ten minims of 1 to 1,000 adrenalin was immediately given hypodermically, and the attack passed off in a few minutes. Both the patient and the doctor were so alarmed that they did not wish to try any further injections. This patient was last heard from two years later and still had attacks of asthma, as severe as ever.

Personally, I consider it poor therapy to mix unrelated substances for hyposensitizing injections. Furthermore, there can be no definite schedule for increasing the doses, as each patient is a law unto himself.

*Case 2*, was a man 27 years of age who had suffered from asthma for 21 years. The attacks were frequent and severe from December to March, but never occurred in summer. A slight eczema was present in childhood. This lesion still occurred between his fingers in winter. Protein sensitization tests showed a very marked reaction to flax only. When questioned after the test, he remembered having an unusually severe attack of asthma after eating "Roman Meal", a breakfast food which contains flaxseed. Flax desensitization was diligently carried out over a period of four months. The first injection of 0.1 c. c. of 1 to 10,000 extract produced a very severe attack of asthma. A more dilute solution was used for a while, and the amount gradually increased. At times slight attacks of asthma occurred and the dose would be decreased. After four months' treatment, the injection of 0.8 c.c. of 1 to 15,000 would produce very slight asthma. The patient thought his asthma was slightly less troublesome than before treatment. The dermatitis between his fingers disappeared. Two years later he said he still had asthma in cold weather and on exertion, but it was of a different character and somewhat less severe than what he had suffered before the injections. The diameter of the wheal produced by flax protein rubbed into a skin scratch was three-quarters of the one which had occurred on the original test before treatment was begun.



Close view of a panicle of flax, showing buds, flowers, and bolls in successive stages of growth, some of the latter being fully matured.

The fact that this man had asthma only in the period from December to March might be explained by a bacterial factor, but on the other hand, the thought occurred to me that possibly it could have been due to his drinking milk from cows fed on dairy feed containing linseed meal. In other words, during the summer the cows would be out on pasture, where as in the winter they would be given dairy feed exclusively, and consequently the milk from these cows would contain linseed protein in the winter but not in the summer. This patient's experience with "Roman Meal" demonstrated conclusively that the ingestion of flaxseed protein was capable of producing severe asthma. The constitutional reaction from the first injection of the flax protein extract could, in all probability, have been avoided by first testing the patient with various dilutions to determine the proper initial dose.

*Case 3*, was a woman 35 years of age who had suffered from rhinitis and seasonal hay-fever for twenty years. Protein sensitization tests showed the following positive reactions: flaxseed + + + +, horse hair + + + +, orchard grass + +, rye + +, daisy +. Later intradermal tests showed the following reactions: flaxseed extract 3.5 cm. in diameter; new linen extract 3 cm. in diameter; old linen extract 1.6 cm. in diameter; silk extract 0.5 cm. in diameter. About an hour after these intradermal tests a severe attack of sneezing developed. No treatment was undertaken at that time, but the following spring a mixture of equal parts of flaxseed, horse hair, orchard grass and rye pollen was prepared and injections given. This patient said that she obtained a fair degree of benefit from two such courses of pre-seasonal treatment.

I feel obliged to again criticise the mixed or "shotgun" treatment. Where

it is necessary to treat with unrelated substances, these treatments should be given separately.

*Case 4*, was a nurse 35 years of age who for the preceding eleven months had had violent attacks of sneezing and lachrymation, which came on almost every morning after she had visited the store room. Protein sensitization tests showed the following positive reactions: flaxseed + + + +, chamois +, cheese  $\pm$ . After four injections of the flax protein extract, starting with 0.1 c.c. of 1 to 10,000, the attacks of sneezing ceased, and had not returned when she was last heard from, nearly three years later. Dr. Nicholson did not have an opportunity of testing out the cutaneous reaction to flaxseed after the injections, but he judged from the result in *Case 2* that it would have been unchanged.

Nothing is said about what was kept in the store room, but the fact that this patient was a nurse makes me think of the possibility of her having come in contact with flaxseed, which is commonly used in the preparation of poultices.

*Case 5*, was a man 58 years of age who had suffered from asthma for a year. Protein sensitization tests showed a very marked reaction to flaxseed only. As treatment, a 1 to 1,000 solution was made up and given by mouth, starting with one minim in water three times daily after meals and increasing every third day by one minim. He took this treatment over a period of three months, but noticed no change in his attacks of asthma. These attacks were intermittent and occurred in about the same frequency and severity as before treatment.

*Case 6*, was a farmer 35 years of age who had suffered from asthma of a very severe type for seventeen years. When questioned regarding the causative factors, this patient stated, among other things, that threshing flax was by far the worst offender. His asthma was much worse in the winter time. Ten years previously he had

left his farm and worked on the railroad for a winter, and during that time he was entirely free from asthma. Protein sensitization tests showed the following positive reactions: flaxseed + + +, buckwheat + +, dog hair + + +, horse hair + + + +, cow hair + + + +, goose feathers +. A mixture of 1 to 10,000 each of flax, dog, horse and cow hair, and goose feathers was prepared for his treatment. A drop of this mixture in a scratch on his arm produced a large urticarial wheal. A 1 to 100,000 solution was prepared, and as his reaction to this solution in a scratch was scarcely noticeable, he was given 0.1 c.c. subcutaneously. The amount of the injection was slowly increased every second day. After the 0.4 c.c. dose of 1 to 100,000 he had slight asthma. The dose was decreased, and no constitutional reactions developed after that. He had no attacks of asthma during a period of a month while he was in the hospital for observation, and he would have continued taking the injections in increasing doses over a period of about six months, but a week after returning to his farm he died of a virulent pneumonia, following exposure to cold.

In addition to my opposition to the mixed treatment, I do not consider that the desensitizing injections should have been given as often as every second day.

Case 7, was a boy 4 years of age who had had asthma for the preceding two years. Protein sensitization tests showed a + + + reaction to flax and also marked positive reactions to a number of other substances. The boy's parents were advised to eliminate from his diet and environment all of the foods and other substances to which he gave positive reactions, but insufficient time had elapsed to know the result.

In a preceding paper<sup>6</sup>, I stated that sensitization to linseed meal, a common component of poultry feed, is one of the rather unusual causes of hay-fever and asthma.

Rowe<sup>7</sup> reported the case of a man, aged 38, who had had an itching ec-

zema on his face, neck, arms, and legs, for three years, appearing each spring and becoming extremely severe by September. Whenever he left his chicken ranch, the eczema would immediately improve. Skin testing gave three plus reactions to artemisia vulgaris and biennis, to ambrosia psyllostachya, and to flaxseed, which was in the chicken mash he was using.

Feinberg<sup>8</sup> stated that flax and its products are occasionally responsible for allergic conditions.

Figley and Elrod<sup>9</sup> reported thirty cases of asthma known to have been caused by the inhalation of finely powdered castor bean dust in the neighborhood of a linseed and castor oil mill. Five of these thirty patients also gave cutaneous reactions of varying strengths to flaxseed, but these were regarded as examples of multiple sensitization, especially as the castor bean reactions so markedly overshadowed the flaxseed reactions.

Thomas<sup>10</sup>, under the heading of Flax, writes as follows:

"Flaxseed, when ground into meal and inhaled, is a possible cause of asthma. It is, however, but seldom used in the modern household except in making poultices. A flaxseed poultice upon the skin of a patient sensitive to its proteins might well be the cause of allergic symptoms. It is also possible that linseed oil may contain enough protein to account for symptoms in a sensitive person exposed to it, as, for example, a painter or occupant of an apartment whose walls have been freshly oil painted. Flax protein for testing and treatment is available for use in cases where sensitivity to linen is suspected."

Balyeat<sup>11</sup> in an article on perennial hay-fever stated that he had found one patient whose symptoms were very much increased on working with

flaxseed, and skin testing proved a definite sensitivity to it. In discussing this paper I made the comment that flaxseed or linseed meal is a common ingredient of chicken mash, and that I had had several patients with severe perennial hay-fever and asthma, whose trouble was due to sensitization to this substance. Dr. Hal M. Davison, in discussing this same paper, said that a fair percentage of cases in Atlanta are sensitive to flaxseed and that they give an extremely marked skin reaction.

Black<sup>12</sup> very recently reported two cases of flax hypersensitiveness, which, because of their pertinent interest, I will repeat in considerable detail.

*Case 1.* A man, aged 23, was given for breakfast a cereal called "Roman Meal" cooked as porridge. He had never eaten this before, and as the first spoonful caused a tingling and burning sensation of his lips and tongue, he asked if the food contained pepper. Another member of the family tasted it without noticing anything unusual. The patient then proceeded to eat the cereal, but as he ate, found that his tongue and throat felt swollen. He drank a cup of coffee, after which the tingling and burning sensations diminished. Within five minutes after he had finished eating, and with almost no premonitory nausea, he vomited. Vomiting was violent and continued. During this period the previously mentioned sensations returned to the lips and tongue and extended to the pharynx, which felt "like it was on fire". It became very difficult for him to talk. At the same time extreme coryza and lachrimation developed, the burning sensation being present in the nose and eyes. The conjunctivae and lids became so edematous as nearly to close the eyes. The disturbances lasted, in all, about three hours, but the most acute stage lasted only thirty minutes. There were two bowel movements, the stools being copious and soft, but there was no diarrhea. Abdominal discomfort was present as a diffuse heavy sensation, so intense as to approach pain in

character. After recovery from the acute stage of the reaction, no ill effects were noted, and on the afternoon of the same day he felt entirely well. Several days later the patient brought in a sample of the food, the composition of which, as stated on the container, is wheat, rye, and flax. Cutaneous tests by the scratch method were performed with the "Roman Meal", and also with the purified proteins of wheat (whole), rye, flaxseed, and flax. Tenth-normal sodium hydroxide was used as a diluent. In fifteen minutes, reactions became apparent with the "Roman Meal", and with flaxseed, which were strongly positive in thirty minutes. At this time the two reactions were alike in size, with wheals approximately 3 cm. in diameter with well defined pseudopodia, and were surrounded by an area of erythema. Wheat, rye, flax, and the control showed no reactions. The reaction from "Roman Meal" subsided within twelve hours, but that from flaxseed was present as a diffused swelling twenty-four hours later. After this reaction subsided, he was tested by the same method to linen and linseed oil (raw). These tests were negative.

The only previous contact this patient had had with flax, as far as was known, was at the age of 4, when flaxseed poultices were applied to a carbuncle on his leg, over a period of about ten days.

*Case 2.* A man, aged 48, was seen by Dr. F. E. Becker in response to an emergency call. He found the patient in bed, very dyspneic and cyanotic. The illness had begun immediately after the patient finished eating a small dish of cooked "Roman Meal" for breakfast. It started with nausea, vomiting, and dull pain in the upper part of the abdomen. The throat felt swollen and "as though it were paralyzed". Phonation was very difficult, and the voice became harsh. During this stage, which lasted from ten to fifteen minutes, respiration became increasingly difficult and was asthmatic in character. Cyanosis developed rapidly. At this time ephedrine sulphate was given by mouth, with prompt relief. As the cyanosis disappeared, a generalized erythema became apparent. There were several urticarial wheals on the abdomen. There



was no fever, coryza, or conjunctival irritation. The disturbances lasted in all about two hours, and cleared up without any lasting ill effects. Because of the similarity between this and the first case, cutaneous tests, with the same technic, were made with wheat, rye, flax, and flaxseed. The reactions to wheat, rye, and flax were negative, but flaxseed caused a very strong reaction which appeared within five minutes, at which time the excess test solution was removed. However, the reaction continued to spread, many long pseudopodia appearing. A wheal which measured 4 cm. in diameter was present at the end of fifteen minutes. The whole flexor surface of the forearm was erythematous.

At the age of 18, this patient had had a severe infection of the foot, which was treated with flaxseed poultices for about two months. Shortly after his recovery from this infection, he began to have sharp attacks of asthma, which would appear and leave suddenly. When he was about 38 years old, he had had an attack somewhat similar to the one described, but milder, which came on several hours after he had eaten buckwheat cakes.

Black concluded that flaxseed apparently causes more violent local and general reactions in the hypersensitive than do most of the other allergic food substances, and that in these two cases there was a history of previous contact with flaxseed in the form of poultices, from which an inference as to the etiology of the hypersensitiveness might be drawn.

#### FLAX AND ITS PRODUCTS\*

\*In preparing this section I have drawn freely from such authoritative sources as Henry and Morrison's book "Feeds and Feeding", and various bulletins of the U. S. Department of Agriculture.

*Flax Plants.* Flax is the common name for plants of the genus *Linum* and for the fiber obtained from the stems of *L. usitatissimum*. This

species, of unknown origin, has been in cultivation from a very remote period. The plant is an annual, with slender stems and blue flowers. Fiber flax and seed flax belong to the same botanical species (*Linum usitatissimum*), but, like sweet corn and field corn, they are of different types. Seed of fiber flax must be sown in order to produce fiber-flax plants, and vice versa. A fiber-flax plant has the characteristic tall stalk (about 3 feet) and few seed bolls, whereas a seed-flax plant has shorter stalks (about 2 feet) and many seed bolls. The flax boll contains ten seeds, when all develop. The cultivation of flax for fiber and the cultivation of flax for seed or oil are two distinct industries. For 138 years flax has been grown in the United States, principally for its seed. The invention of the cotton gin in 1792 and the consequent cheap production of cotton fiber practically ended the flax-fiber industry in this country. Seed flax in the United States is grown chiefly in North Dakota, Minnesota, South Dakota, and Montana, ranking in production in the order named.

*Flax Fiber.* This ranks next to cotton in importance among the vegetable fibers. The straw of seed flax grown in the Northwest does not yield a fiber suitable for spinning. Approximately 80,000 tons of flax straw are used in the United States each year in the manufacture of insulating material, tow for upholstering, and coarse wrapping cord. It is also used at times as feed for livestock. Fiber flax yields both spinning fiber and seed suitable for sowing, oil production, or feeding. The preparation of spinning fiber from flax straw is a process in-

volving skilled labor and special machinery. After harvesting the flax, the various operations are known as threshing, retting, breaking, scutching, and hackling. The flax fiber is spun in the flax-spinning mills to make sewing thread, shoe thread, harness thread, fishlines, fish nets, and twines.

*Linen.* Linen thread or yarn is woven to make the various linen materials, the most important of which are: art linen, batiste, bird's eye linen, cambric, collars and cuffs, damask, diaper, dress linen, fire hose, glass-cloth, handkerchief linen, huckaback, lawn, linen crash, sheeting, shirting, table linen, and toweling. Lint is a flocculent material procured by raveling or scraping linen, which is sometimes used for wadding and batting, or for dressing wounds and sores.

*Flaxseed.* The seeds of the flax plant are small, flat, oblong, brown seeds. Although the terms flaxseed and linseed are used more or less interchangeably, some authorities wisely prefer to limit the term flaxseed to the seed of the flax plant prior to the expression of the oil, and use the term linseed only to designate the products of the seed, namely, oil, cake, and meal.

For ten years previous to 1909 the United States produced a surplus of flaxseed, and considerable quantities were exported to Europe. From 1909 to the present, however, flaxseed production in the United States has averaged slightly less than half of the consumption, and in recent years large quantities have been imported from Argentina and Canada.

Analyses of mature flaxseed show it to contain from 30 to 45 per cent of

oil, and an average of 22.6 per cent crude protein. Flaxseed also contains a hydrocyanic-acid-producing glucoside which, when acted upon by an enzyme in the seeds, yields the poison, prussic acid. On account of the high commercial value of the oil it contains, flaxseed is rarely used for feeding stock other than calves. Dairy calves are made sick at times by feeding them flaxseed which has been allowed to stand in the presence of water, thus permitting the enzyme to act and produce free hydrocyanic acid. Some authorities deny this, stating that the trouble is due to an admixture of some poisonous seed such as the castor bean. Nevertheless, an analysis of flaxseed made very recently at the office of the Food, Drug, and Insecticide Administration of the U. S. Department of Agriculture showed it to contain 650 parts of HCN per 1,000,000. Therefore, in making gruel or mash from untreated flaxseed, it is advisable to use boiling water and keep the mass hot an hour or two, to destroy any prussic-acid-forming enzyme in the seed.

In medicine, flaxseed is used as a demulcent and an emollient. Its infusion, flaxseed tea, is used internally in catarrhs of the respiratory mucous membrane, in enteritis and dysentery, and in irritation of the kidneys or the urinary passages. Flaxseed poultices are quite commonly used in the treatment of localized inflammation.

"Roman Meal" is stated by its manufacturers, the Roman Meal Company of Tacoma, Washington, to be a balanced food made from whole berries of wheat and rye, with bran and sufficient especially prepared tasteless flax-

seed to neutralize by its healing properties the irritating effect of bran upon the lining of the digestive tract. I have been told that there is an identical or similar preparation put out by a Canadian concern.

"Flaxolyn", a proprietary laxative manufactured by the Herbal Flaxolyn Corporation of Brooklyn, N. Y., is said to contain, among other things, baked flaxseed as a demulcent and local soothing agent. This same company also markets an emulsion containing flaxseed.

*Linseed Oil.* The oil of the flax seed is either extracted by the "old process", through crushing and pressure, as in the production of cottonseed oil, or by the "new process" in which it is dissolved out of the crushed seed with naphtha, the residue in either case being variously termed linseed oil meal, linseed meal, or simply oil meal. Flaxseed yields about  $2\frac{1}{2}$  gallons ( $18\frac{3}{4}$  pounds) of oil to a bushel (56 pounds) of seed. Oil produced from immature seed is a greenish brown, while that from ripe seed has a yellowish brown color. Ripe seed produces a greater amount of oil as well as a finer quality. Linseed oil is used extensively in the manufacture of paints and varnishes, linoleum, oilcloth, printers' ink, patent leather, imitation leather, oilsilk, and many brands of furniture polish.

*Linseed Cake and Meal.* The residue left after the oil has been extracted is known as linseed cake or, if ground, as linseed meal. One bushel of flaxseed (56 pounds) produces about  $37\frac{1}{4}$  pounds of linseed cake. Practically all linseed meal, especially in the United States, is made by the

"old process". Old-process linseed meal contains approximately 34 per cent of crude protein and 6 to 9 per cent of fat or oil, whereas new-process meal carries an average of 3 per cent more crude protein but contains only 2 to 3 per cent of fat or oil. The prussic-acid-forming enzyme in flaxseed is destroyed by the heat to which the ground seed is ordinarily subjected in both the old and the new process of oil extraction. There is no more healthful feed for limited use with all farm animals than linseed cake or meal, with their rich store of crude protein, slightly laxative oil, and mucilaginous, soothing properties. Linseed meal is one of the most popular feeds for dairy cattle, and is also a common ingredient of poultry feeds. It is excellent for horses, and is also one of the best protein-rich supplements for fattening sheep and beef cattle, and gives good results with swine when fed in proper combination. In this country the demand is chiefly for linseed meal instead of the unground cake, probably owing to the fact that, mixed with other concentrates, it is fed mostly to dairy cows.

A linseed solution is quite commonly used in beauty parlors to hold the hair in place after it has been waved.

#### CASE REPORTS

Without searching through my case-record files, I can recall several patients with typical linseed meal sensitization, and I will briefly report these cases.

*Case 1.* A young woman, aged 29 years, was referred to me in June, 1922 with bronchial asthma of four years' duration. Her attacks started with violent sneezing. During the attacks, her eyes itched severe-

ly and became swollen. When I questioned her carefully, she told me she believed that at least one of her attacks had been caused by an orris root shampoo. A cutaneous test with orris root protein gave a marked positive reaction, and all other skin tests were essentially negative. She was advised not to have any more orris root shampoos, and to avoid using powders or other cosmetics containing orris. Also, she was given orris root desensitization. As a result, the asthma promptly left her and she remained entirely free for a period of four years.

This patient consulted me again in February, 1927 with asthma which had recurred about two months before. She stated that she was still avoiding orris root in all forms. During the four year period which had elapsed since I first treated her, she had married and moved to the country where they raised their own chickens. They fed the chickens a prepared mash, which she said made her sneeze when she handled it. The mash was found to contain wheat bran, cocoa shell meal, linseed meal, alfalfa meal, meat meal, and powdered milk. A cutaneous test was made with each of these ingredients and they were all negative with the exception of linseed meal, which gave a definitely positive reaction. It is interesting to note that a skin test with a commercial flaxseed protein gave only a doubtful reaction. Tests with chicken feathers and other substances were all negative with the exception of orris root, which still gave a positive reaction although it was definitely smaller than when I first tested her. This patient's asthma disappeared after eliminating the chicken mash containing linseed meal, and when last heard from she was still perfectly well.

*Case 2.* A man, 34 years of age, consulted me in October, 1926 with perennial hay-fever. He had terrible itching of the eyes, sneezing, running of the nose, and headaches, and recently had developed some coughing and wheezing. The discharge from his nose was thin, clear water. He was a carpenter by trade, but had always lived in the country and been around chickens. He had never had any of this trouble while away from home or at work. He fed the

chickens mash, which he had noticed would make him sneeze. The mash contained alfalfa meal, meat meal, middlings, bran, linseed meal, ground oats, and corn meal. He was tested cutaneously with each of these ingredients and gave a marked positive reaction to linseed meal, the other components being negative. In this case also, a skin test with a commercial flaxseed protein gave only a doubtful reaction. Skin tests with chicken feathers and various other substances were all negative. This patient's non-seasonal hay-fever left him just as soon as he discontinued using a chicken mash containing linseed meal.

*CASE 3.* A woman, 55 years old, was brought to me in September, 1929 with bad asthma and non-seasonal hay-fever of about 15 years' duration. With the attacks, her eyes, nose, and face got very red and swollen, and she sneezed and wheezed a lot. She thought that drinking milk made her worse. These attacks made her terribly nervous, and at times were accompanied by headache, nausea and vomiting. She lived on a farm and in this connection stated that she could not go around chicken feed, and that flax also bothered her. A cutaneous test with linseed meal gave an enormous reaction, the urticarial wheal being about 2 inches in diameter. Tests with commercial flax and flaxseed proteins gave only a doubtful reaction to the former, but a marked, positive reaction to the latter. Skin tests with a large number of other substances showed her to be multiple-sensitive, but none of these other reactions could compare with the one to linseed meal, which remained plainly visible on her arm for several days after the test. Tests with milk proteins were completely negative, but it is perfectly possible that she had been getting linseed protein in the milk, as linseed meal was used routinely in their dairy feed. The chicken feed they used also contained linseed meal. I advised the discontinuance of all feed containing linseed, and in addition decided to give this patient linseed treatment, for its specific as well as non-specific desensitizing effect. A 1 to 20 extract was prepared by adding 5 grams of linseed meal to 100 c.c. of Coca's fluid.<sup>13</sup> After this

extract was Berkefeld filtered and examined for sterility, 1 to 200, 1 to 2,000, and 1 to 20,000 dilutions were prepared, using Coca's fluid as diluent. When I tested her with these dilutions, she gave a positive reaction to the 1 to 2,000, and a practically negative reaction to the 1 to 20,000. Treatment was started with 0.05 c.c. of the 1 to 20,000 extract, and the dose was gradually increased at weekly intervals. After taking only ten injections, this patient was so well that she discontinued treatment, and when heard from very recently, reported that she was entirely free of all symptoms of asthma and hay-fever.

I have three other patients under my care at the present time, who give marked, positive, cutaneous reactions to linseed meal. One of these patients has a dermatitis and seems to be sensitive only to linseed. The other two have chronic perennial asthma, and are both multiple-sensitive. These three patients have not yet been sufficiently studied, to determine the clinical importance of their sensitization to linseed meal, but it is interesting to note their lack of reaction to skin tests with commercial flax and flaxseed proteins. The patient with dermatitis gave no reaction to flax protein, and only a slight or doubtful reaction to flaxseed protein. One of the patients with asthma gave no reaction to flax and only a slight reaction to flaxseed, but gave a definitely positive reaction to my linseed meal extract. The other patient with asthma gave no reaction to skin tests with commercial flax and flaxseed proteins, and yet gave definitely positive reactions to cutaneous

tests with "Roman Meal", "Flaxolyn", and my linseed meal extract.

#### SUMMARY

The vast literature on allergy contains occasional references to sensitization to flax, flaxseed, or linseed, and these references are reviewed somewhat completely.

A general description of flax and its products is given to show the numerous ways in which a person hypersensitive to the flax proteins may come in contact with them.

Several typical cases of linseed meal sensitization are reported by the writer.

#### CONCLUSIONS

Although sensitization to flaxseed or linseed is one of the less commonly encountered forms of hypersensitivity, it is of sufficient importance to merit careful consideration in diagnosing and treating asthma, non-seasonal hay-fever, dermatitis, or urticaria, especially in persons such as farmers or nurses, who come in contact with these substances.

Sensitization to the protein of flaxseed or linseed is usually very marked, and the best method of detecting it is by means of the cutaneous or "scratch" test, using ordinary linseed meal and moistening it with a drop or two of tenth-normal sodium hydroxide solution.

Specific desensitizing injections of a linseed meal extract may be given with perfect safety, providing sufficient care and judgment are used in determining the initial and subsequent doses.

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## Avitaminosis Complicated by Cestodiasis; Case Report\*

By J. A. McINTOSH, M.D., F.A.C.P., *Memphis, Tenn.*

**A**VITAMINOSES occur in man and other animals when diets poor or deficient in vitamins are eaten, but attention to protozoa and metazoa as "Vitamin robbers" in the intestinal tract capable of inducing avitaminosis in the host if the diet is below normal therein has not been recognized and given emphasis.

We are familiar with the saying that a good appetite in the presence of malnutrition is suggestive of tape worm infestation, and such metazoa as the broad tape worm of the fish and the hookworm are known to cause secondary anemias, but they are not generally regarded as "Vitamin robbers" inducing the diseased state of avitaminosis. We have seen individuals harboring metazoa and protozoa with signs and symptoms, mild to severe, of avitaminosis and it has caused us to regard them as "Vitamin robbers" and to place emphasis upon the association of the infestation and the disease state.

Proof that metazoa and protozoa require vitamins for growth and reproduction is being sought by feeding experiments in the laboratory at the St. Joseph's Hospital. Some of the protozoa have been cultured with success by

us in media containing water soluble vitamins. We have used a culture of the *Waskia intestinalis* to determine the growth promoting and reproducing rate in blood serum, urine, spinal fluid, saliva, and liver extract, and have observed marked variations. We found a lesser rate of growth in urine from individuals with mild avitaminosis than in normal urine. From this it would seem that such an animal could be used to determine the quantity of growth promoting vitamin in any given fluid. Certainly an accurate test is desirable to quickly determine mild avitaminosis in man before it is written on the face. (See picture).

The established distinction of vitamins into A,B,C,D. and E. groups detectable when absent in diets by causing signs and symptoms referable to epithelial, nervous, endothelial, osseous, and reproductive tissues is of service in selecting diets for treatment of xerophthalmia, beriberi, scurvy, pellagra, rickets, and sterility, but the need of early diagnoses in the human is obvious. According to Statt<sup>1</sup> the albino rat is the most suitable animal in testing for vitamin A; the pigeon or chicken for B; the guinea pig for C; the rat or puppy for D; but so far as we know the *Waskia intestinalis* has not

\*Read before the Memphis and Shelby County Medical Society April 15, 1930.

been utilized for such tests before. We have tested certain commercial foods labeled concentrated vitamins with the *Waskia intestinalis* using water soluble vitamin B from the Irish potato as control solution. We expect to report data at a later date.



FIG. 1. *Avitaminosis (Pellagra) Complicating Cestodiasis*. Repeated feces examination showed ova of *Hymenolepis nana* (tapeworm). Observe the characteristic symmetrically distributed eczema of pellagra on face (band like), forearms, and dorsal aspect of hands and feet. Note the anxious expression.

If Cestodes, as do higher forms of animal life, require vitamins for growth and reproduction, they obtain them from the food in the host, and the host, as suggested by the following case report of associated infestation and the state of avitaminosis.

Baby L. A., white female, age  $2\frac{1}{4}$  years, was admitted to the St. Joseph's Hospital on 5/15/29 to the service of Dr. K. M. Buck, complaining of an eruption on face, neck, hands, and feet. She is the youngest of six children of a poor family in Arkansas. Her mother, whom she nursed up to three weeks prior to admission to the hospital, died of childbirth complications. The father noticed small multiple eruptions on her neck at this time. These gradually became confluent and spread and were crusted as shown in the accompanying photograph. Her diet before admission consisted of pregnant mother's milk, corn bread, dried beans, Irish potatoes, and salt pork meat. None of the other children was similarly affected and all subsisted on the same diet except mother's milk. There had been no previous illness except measles at one year of age.

The physical examination revealed an erythematous, brownish, moist crusted eruption as stated in the complaint with brownish staining of the adjacent skin. The facial expression was stoic, and she was not responsive to sympathetic advances. There were fourteen well developed teeth, and the tongue was clean, red and shiny. The hair and skin were dry and lacked normal lustre. The balance of the examination revealed nothing abnormal. The bony skeleton was not X-rayed. Her admission weight was 19 9/10

pounds, and the departing weight 22 $\frac{3}{4}$  pounds. During the hospital stay of 56 days the temperature was never over 100 degrees Fahrenheit. Between 5/15 and 6/1 we made eight total white and differential leukocyte counts averaging 17,000 with eosinophils 3.2%; neutrophils 60%. One hundred defecations were charted and of these forty were examined microscopically. Ova of the *Hymenolepis nana* (see fig. 31) were found constantly up to 5/28/29 and none thereafter though the specific

worm medicine was not given until 7/1/29. Charcot Leyden crystals were present in the stool examined 6/11/29. The blood flocculation test for syphilis was negative. The urine was negative except for acetone bodies upon admission.

Due to the absence of atrophic lesions one medical consultant said that the condition was not pellagra. Another stated that it was pellagra with atypical features.

The diet fed at the hospital was com-



FIG. 2. *Avitaminosis (Pellagra) Complicating Cestodiasis.* A posterior view of patient.

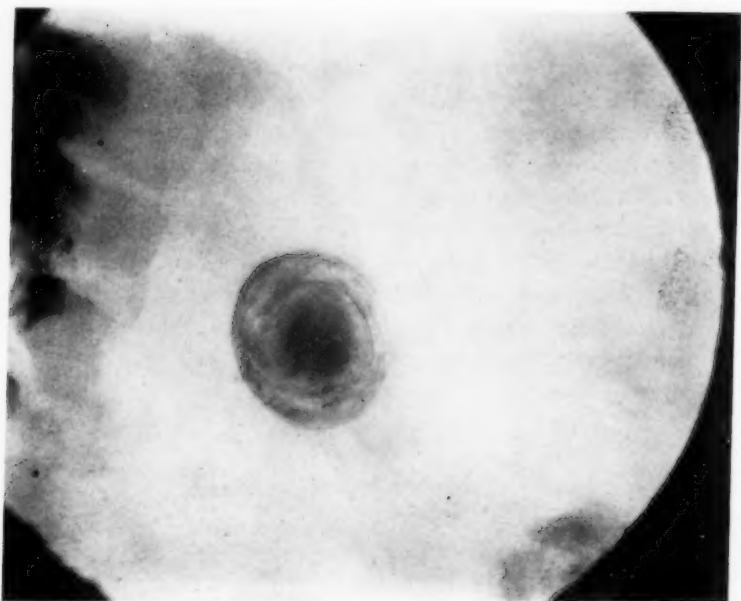


FIG. 3. *Oocyst of Hymenopelis Nana*. Present in feces of Baby L. A., 16mmx10 magnification.

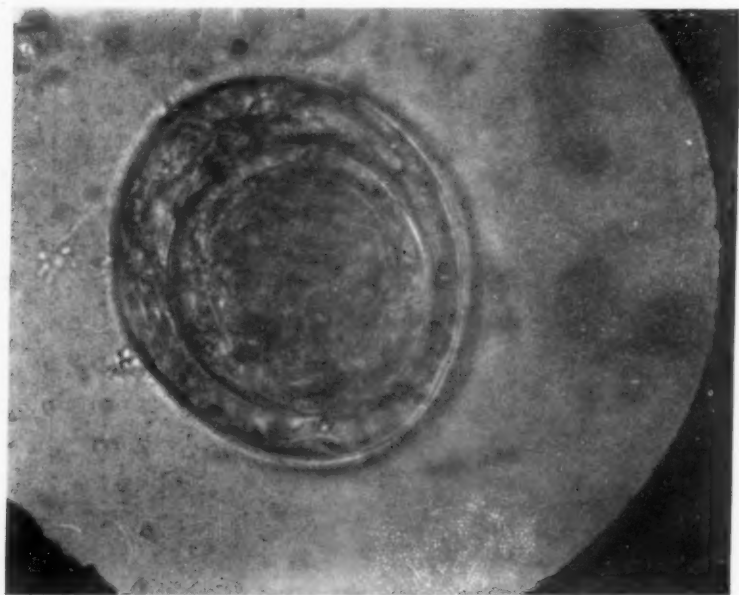


FIG. 4. *Oocyst of Hymenopelis Nana*. Present in feces of Baby L. A., 4mmx10 magnification.

posed of broth, cereals, sweet and buttermilk, cocoa, vegetable soup, custard, orange juice, crackers, jello, rice, spinach, potatoes, eggs, peas, and chicken. Olive oil was applied locally to eruption. Eight grains of sodium cacodylate were given in 16 sub-cutaneous doses. Brewer's yeast and cod liver oil labeled vitamins A, B, C, and D, were given t. i. d. Definite improvement followed the ingestion of maltine with cod liver oil. Calomel, aspidium, magnesium sulphate, and tea enemas were given, the latter to eradicate the taenia though the ova had disappeared from the stools following the concentrated vitamin diet. The anterior and posterior view photographs indicate the improvement fourteen days after admission.

The adult worms were not found though repeated search of the stools were made.

#### DISCUSSION

The ova found in the feces correspond to the description of the dwarf tapeworm *Hymenolepis nana*. This parasite, according to Simon<sup>2</sup>, may cause loss of appetite and diarrhea, and in some instances, epileptic convulsions. A similar parasite has been found in rats and are regarded by Hall<sup>3</sup> as identical to ones found in the human. Development in the human takes place in the intestinal canal. The young worm leaves the egg, enters a villus of the mucosa and in 62 hours develops into mature bladder worms (cysticoid form). This breaks and the liberated worms attach themselves to the mucosa and become adult worms (Strobiliolate forms) in two weeks. The adult is 4-8 mm. long with a bell shaped head set with 24-28 hooklets. The segments are yellowish and are four times as broad

as long and contain colorless round and oval eggs having an outer and inner envelop. They measure 68 micra in diameter. The oncosphere with hooklets are within the inner capsule. The ova of other cestodes do not have the outer capsule and the transparent material between. The common hosts are children.

The type of avitaminosis present in this case report corresponds to vitamin



FIG. 5. Avitaminosis. Two weeks after treatment with foods rich in Vitamin "B." Note increase of animation in face and residual stains from eczema.

B complex deficiency or pellagra. Vitamin B complex or the growth promoting vitamin is water soluble and contains fractions separable by heat<sup>4</sup>. The heat labile fraction is anti-neuritic and is called vitamin F or B-1. The heat stable fraction is called vitamin G or B-2 or anti-pellagic. Deficiency in the diet of the heat stable fraction of vitamin B causes retardation of growth, loss of weight, soreness of eyes, mouth, nose, weakness, and lethargy. Diarrhea is common. With less deprivation skin symptoms are more prominent with bilateral symmetrical positions such as were present in Dr. Buck's patient.

"The rapidity with which symptoms of vitamin B deficiency becomes apparent indicates that the body has only a limited capacity for storing this vitamin<sup>6</sup>. We cannot explain why diets reinforced with concentrated vitamin B caused the ova to disappear from the stools in this patient. A similar observation has been made in flagellosis (*Chilomastix mesnili*). At first they increase, then diminish in the feces after a diet of yeast fed several weeks.

#### CONCLUSIONS

Because of the frequent association of mild to severe avitaminosis in indi-



FIG. 6. (*Avitaminosis*.) Posterior aspect two weeks after treatment with foods rich in Vitamin "B."



viduals harboring metazoa and protozoa and the clinical improvement following administration of concentrated vitamins and the ready growth in artificial media containing water soluble extracts, we therefore regard them as "vitamin robbers" and capable of inducing certain deficiency diseases such as pellagra.

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## Tetralogy of Fallot: Report of a Case With Bacterial Endocarditis of the Pulmonary Valve and Collapse of Both Lungs\*

By ROY S. LEADINGHAM, M.D., F.A.C.P., *Atlanta, Ga.*

**A** WELL developed and well nourished intelligent white female child fifteen years of age with cyanosis of face and extremities, entered the hospital June the first complaining of dyspnea, nausea, and vomiting. She stated that she had been cyanotic all her life, but more since an attack of influenza the preceeding Christmas. Dyspnea, which formerly had been present only after unusual exertion, also became more distressing after this illness. For six months previous to admission to the hospital, she had had repeated attacks of swelling of face and extremities, and received treatment for kidney trouble because of the presence of albumin in her urine.

Her family history was negative, and previous illnesses included measles, mumps, chicken pox, whooping cough, and pneumonia. Her tonsils had been removed when she was ten years of

age. Her father stated that she was a full term baby, began walking and talking at the usual time, and attended school with others of her age until the onset of her last illness.

She was a well developed child resting quietly in bed in no apparent discomfort. Her temperature was 96 F; pulse 90, regular and of good volume; and respiration 18. Her blood pressure was 120/80. There was extreme cyanosis of face and extremities and moderate clubbing of fingers and toes. Her pupils reacted equally to light and accommodation. The retinal vessels were engorged and tortuous, but no hemorrhages were present. The cervical glands were not enlarged.

A broad diffuse cardiac impulse was visible over the precordium, and there were visible pulsations of the superficial veins of the chest and neck. PMI was 10cm to the left of the midsternal line in the fifth interspace. LBD was 13cm and RBD 4cm from the midsternal line. There were no palpable thrills. To the left of the sternum the first sound of the heart was partially replaced by a moderately rough, blowing systolic murmur, maximal in the

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From the medical service of the Georgia Baptist Hospital and the Department of Medicine, Emory University, School of Medicine.

Illustrations by Dr. P. F. Lineback, Dept. of Micro-Anatomy, Emory University, School of Medicine.

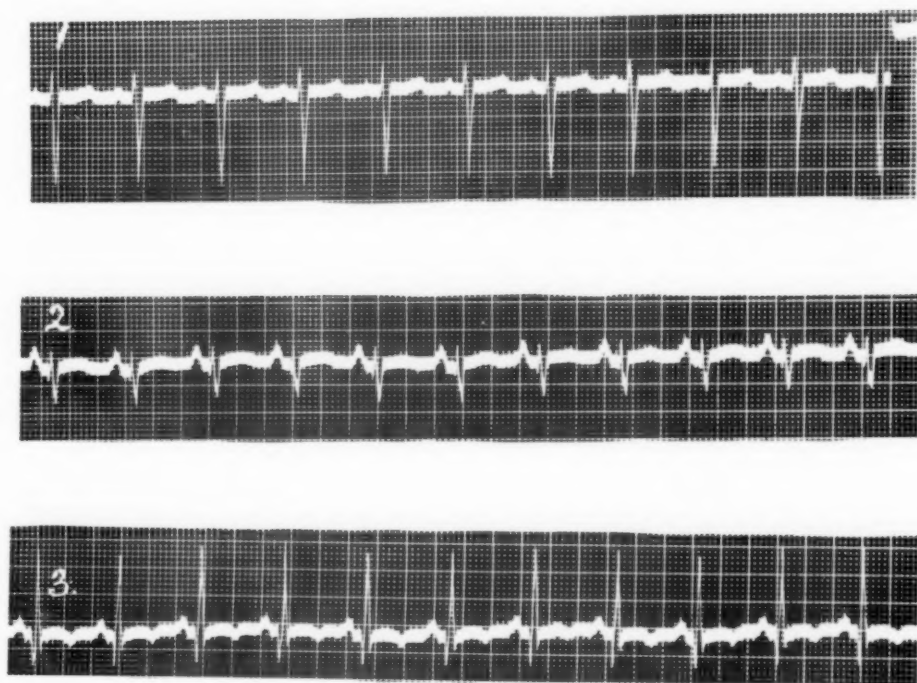


FIG. 1. Electrocardiogram showing right axis deviation. (Dr. J. E. Paullin)

3rd and 4th interspaces. It was transmitted to the left midclavicular region but not to the vessels of the neck. Liver dullness extended from the right fourth interspace to 4cm below the costal border.

Teleo of the heart at seventy-two inches showed the following dimensions according to the Bardeen scale; median right 3cm; median left 10.5 cm; oblique 14.5 cm; aortic arch 5 cm; greatest transverse of heart 13.5 cm; greatest transverse of chest 22.5 cm. In the left oblique position, the retrocardiac space was obliterated by the enlarged heart. The electrocardiogram recorded right axis deviation.

For the first three months in the hospital her temperature rarely reached normal and varied from 96 to 98 F.

Two blood cultures were negative. There was 50 mg. non-protein nitrogen, 25 mg. urea nitrogen, and 2 mg. creatinin in 100 cc of blood. Blood viscosity was 11. Bleeding and coagulation times were normal. Urinalyses were at all times negative except for large amounts of albumin in all specimens. On admission, the red blood count was 6,000,000 and hemoglobin 100 (Sahli). With no apparent change in her general condition, dyspnea and cyanosis gradually increased and two months after admission the red cell count reached 10,910,000 and hemoglobin 130. Because of dyspnea and cyanosis, she was given oxygen two or three times daily and about two weeks later, on August 12th, the cell count had gradually decreased to 8,590,000

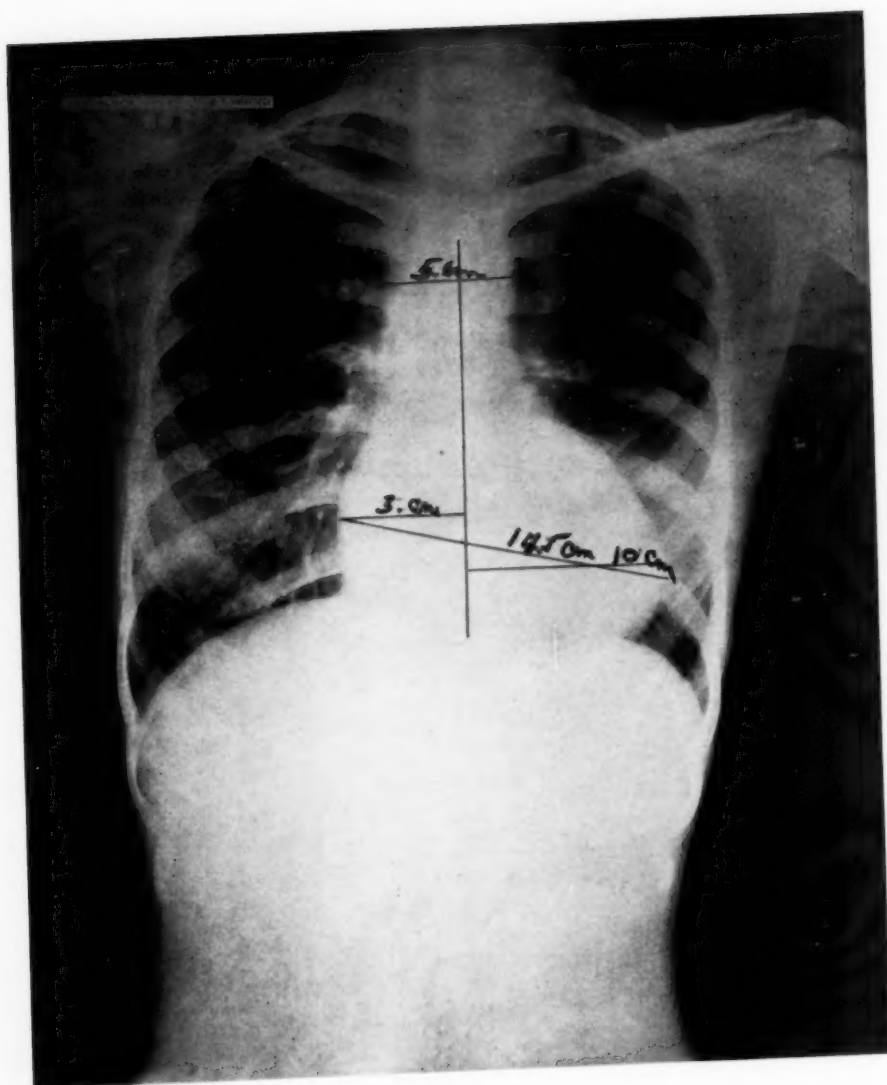


FIG. 2.

and hemoglobin 107. At this time, there were only 2,850 leukocytes with neutrophils 45%, small mononuclears 50%, eosinophils 3%, and basophils 2%. Shortly thereafter she suffered an attack of acute heart failure. Her pulse became very weak, rapid, and irregular and she was very dyspneic. Oxygen was discontinued. She was digitalized and afterward received two grains of digitoxin daily until a few days before her death. On August 21st, the red cell count was 9,840,000 and hemoglobin 120. There were 5,550 leukocytes. Oxygen was resumed because of dyspnea and ten days later there was a decrease of only 100,000 red cells but the leukocytes were down to 2,650. At this time there was 85mg. of non-protein nitrogen in 100 cc of blood.

Early in September her temperature became a little higher and varied from 96 to 99.6 F. For ten days she frequently coughed up blood streaked sputum and was occasionally nauseated. Her face, including eyelids, became swollen and her extremities very cold. She was more cyanotic and had great difficulty in breathing. Shortly after this attack she seemed very much better and improved so rapidly that she wanted to get out of bed. She sang, read, and said that she felt better than at any previous time in the hospital. This feeling of well being lasted about a month. She had few brief periods of dyspnea relieved by oxygen which was then given only when indicated for her comfort. At one time the red cell count reached 12,000,000, but during the month of October varied between 9,000,000 and 10,000,000. Early in November she became listless and drowsy. She spat up blood streaked sputum

more frequently. Dyspnea and cyanosis also increased.

On the day of her death, November 11th, she awoke in the morning feeling quite well. Her temperature was 98 F, pulse 100 regular and of good volume, respiration 20. At 11:40 A.M. she had a sudden attack of dyspnea and called for oxygen which gave her some relief. At 2:00 P.M. her pulse was 120 and respiration 22. She was more cyanotic. At 5:45 P.M. respiration was 28 and pulse 120. At 5:55 P.M. she ceased to breathe.

The clinical diagnosis at the time of death was congenital heart disease with septal defect and pulmonary stenosis.

An autopsy was performed an hour after death and showed collapse of both lungs and passive congestion of liver and spleen. Culture from the hearts blood after several days incubation showed no bacterial growth.

The heart weighed 328 grams. It was quite spherical in shape and the apex was on the right side of the septum. The greatest transverse diameter was 10 cm, of which 6 cm was right ventricle. The right auricle was larger than the left. There were two left and one right pulmonary veins. The aortic valve measured 5 cm, mitral valve 7 cm, tricuspid valve 10cm, and the pulmonary valve 2 cm. The pulmonary valve had two cusps upon which was a vegetative lesion that practically occluded the lumen of the pulmonary orifice. About 2 cm beyond the valve there was a similar though smaller lesion upon the wall of the pulmonary artery. The right ventricle measured 1.5 cm and the left 2 cm in thickness. The foramen ovale was patent and 3mm in diameter. In the region of the pars

membranaceum there was a large septal defect 3 cm in diameter, bounded below by the upper margin of the inter-ventricular septum 7mm in thickness and above by the opening of the aorta which received blood from both the right and left ventricles. It was separated from the pulmonary orifice by a thick muscular wall 1 cm in thickness which extended downward 3 cm from the pulmonary valve and with the anterior ventricular wall formed an infundibulum 3mm in diameter leading

from the right ventricle into the pulmonary artery.

Interest in congenital heart disease has been recorded in many observations upon single and combined malformations of the heart, with and without endocardial infections and other associated anomalies. Peacocks "Treatise on Malformations of the Human Heart" was the first clinical and pathological review of the subject in the English language. After his death, his collection became the property of

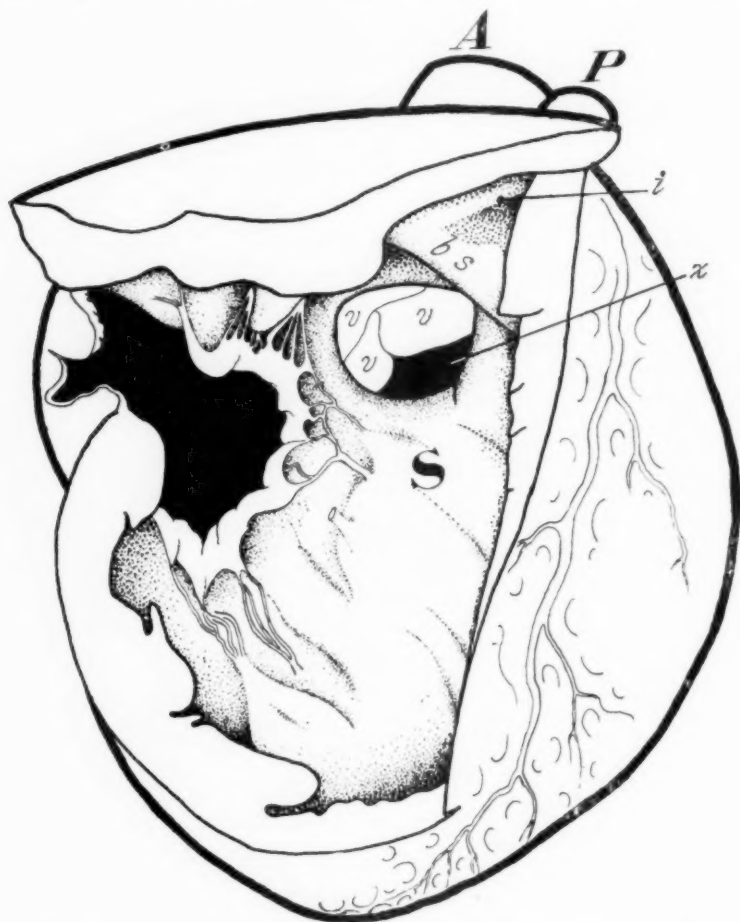


FIG. 3. Heart of Case Reported. X—interventricular septal defect. b s—bulbar septum. i—infundibulum leading to pulmonary artery from right ventricle.





FIG. 4. *Development of Bulbus Cordis.* 2-3, *a* and *b*—lateral swellings which fuse and form the bulbar septum. 4—diagrammatic representation of the closure of interventricular foramen.

the museum of the Royal College of Surgeons of England and furnished a large number of the 270 specimens studied and reported by Keith<sup>1</sup> in 1909. Since that time, many worthwhile contributions have appeared in medical literature and among them an exhaustive monograph by Abbott<sup>2</sup> takes rank as a recent comprehensive study of reported cases.

It is the opinion of most observers that congenital defects of the heart represent faulty or arrested development occurring before the eighth week of embryonic life, at which time the heart in miniature is completely formed. In Abbott's study of 850 cases, 17% were associated with malformations of other parts of the body and some with mental deficiencies. Cases of fetal endocarditis occurring in the course of maternal infections are recorded. Rarely are there histories of familial tendencies to heart anomalies. Cunningham<sup>3</sup> suggested that alcoholism and drug taking might be factors in their production, but this and the theories involving maternal impressions and trivial injuries sustained by the mother during pregnancy have been quite generally discarded.

In 1907, Peter Thompson identified and described the development of the *bulbus cordis* in the human heart. Within its lumen in the 5 mm embryo four longitudinal swellings arise. The two lateral thickenings later fuse, and the later, spiral, clock-wise movement of the bulb and ingrowth of connective tissue eventually divide the aorta from the pulmonary artery, placing the opening of the former over the left ventricle and the latter over the right.

While this development is taking place, the interventricular septum begins to grow upward from the base of the ventricular cavity to join the endocardial cushions. The union of these two structures at about the seventh week forms a temporarily incomplete partition between the right and left ventricles and the lower border of the interventricular foramen, which has as its upper boundary the proximal margin of the bulbar septum. The formation of the septum membranaceum which later closes this foramen is said, therefore, to depend upon the proper fusion of the descending bulbar septum with the upper margin of this dividing wall. Keith and Greil were the first to suggest that the malformations which include interventricular defects at the base of the septum in the region of the *pars membranaceum* represent imperfect closure of the interventricular foramen and are due to an arrest in the development of the bulb. Such defects seldom occur alone, but associated with pulmonary stenosis, dextroposition of the aorta, and right ventricular hypertrophy, constitute a tetralogy described by Fallot as the most common combination of defects found in individuals living beyond the age of childhood. Rokitsansky suggested that the anomalies resulted from a deviation of the bulbar septum with consequent alteration in the size of the great vessels. Others affirm that they are due to the persistence of the reptilian right aorta. Independent defects have been explained as primary arrestments in growth of unknown origin.

Symptoms of congenital heart diseases are usually present from birth,

but occasionally may not be manifest until adolescence or later. The chief diagnostic features are cyanosis, clubbing of fingers and toes, cardiac murmurs, and early hypertrophy.

Congenital cyanosis differs from cyanosis of the later stages of acquired heart disease in that it may exist for many years without any sign of heart failure. With clubbing of the fingers and dyspnea it is one of a triad of symptoms aforesaid known as cyanopathy or morbus coeruleus. It varies according to the character of the defect, from a slight bluish tinge appearing upon exertion to extreme purple discoloration about the cheeks and mucus membranes. Extreme grades are found where there is interference with the circulation to the lungs or where the blood from both ventricles enter the circulation through the aorta. In independent patent foramen ovale it usually is slight or absent until it occurs as a terminal condition.

Associated with cyanosis there may be more or less increase in the number of red cells and the percentage of hemoglobin; and the urine may contain a large amount of albumin.

Dyspnea may be present only after exertion, or associated with other symptoms of heart failure become a prominent symptom of myocardial insufficiency.

The heart is usually considerably enlarged. The left border of dullness may extend well beyond the mid-clavicular line in the 5th or 6th interspaces, and the right border also may extend beyond normal limits. Thrills may or may not be present. In septal defects, a systolic murmur is usually found along the left border of the sternum.

It may sometimes be heard in the subscapular region. Murmurs are variously described according to their volume and character of sound.

Most cases of congenital heart disease die before the end of adolescence. Bacterial endocarditis is the most common cause of death. White and Sprague<sup>4</sup> reported the longest lived case on record. The patient was a noted musician who lived to be sixty years of age and died in coma following an attack of complete hemiplegia, "the heart carrying on a satisfactory circulation to the end."

#### SUMMARY

1. A child of normal mental and otherwise normal physical development, who passed through several acute illnesses and took part in usual childhood activities, lived until past fifteen years of age with a functioning tetralogy of Fallot.

2. Subacute bacterial endocarditis of the pulmonary valve, probably the result of an acute respiratory infection eleven months before, eventually caused occlusion of the narrow pulmonary orifice which was followed by collapse of both lungs and sudden death.

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## Syphilis of the Stomach—A Study of Eight Cases\*

By JOHN B. FITTS, M.D., F.A.C.P., *Atlanta, Ga.*

**V**ISCERAL syphilis has become of increasing interest and importance in recent years due to more accurate diagnosis, and to an appreciation of its wider incidence.

Lesions of tertiary syphilis manifesting themselves in the cardio-vascular and central nervous systems are being more and more emphasized today. The gastro-intestinal tract is less often affected, perhaps, by the spirocheta pallida than any of the viscera. Gastric symptoms in syphilis may be many and varied, they may be independent and superimposed upon an existing syphilis, or the expression of symptoms of central nervous system lues, as gastric crises, or reflexly from syphilis of other viscera. The cases studied in this series, however, refer to the actual involvement of the stomach by the syphilitic process, so-called gastric syphilis.

Eusterman divides the history of this subject into three periods, namely (1) The post-mortem period extending up to 1905, characterized by the extreme rarity of cases. (2) The period of 1905 to 1910, characterized by the clinical classification of cases, and the (3) period from 1910 to the present when the classification of cases were more accurately placed by the Wasserman reaction and the X-ray.

\*From the Department of Medicine, School of Medicine, Emory University.

The material from which this study is made offers a somewhat different approach than that found in the literature on this subject. The material used is derived from the medical wards of a hospital where the admission of the Southern negro is utilized for teaching purposes. This hospital was opened eight years ago, and to date has had 35,000 admissions.

Southern clinicians have long been aware of the tremendous incidence of syphilis among the negro race. Those of us working in the medical ward have been impressed with the large number of cardio-vascular and central nervous system luetics. As the gastro-intestinal tract is less often involved by syphilis, it was thought that it would be of interest to ascertain the incidence of gastric syphilis occurring in this type of clinical material. A routine Wasserman is done on all patients, and of all blood specimens submitted to the laboratory thirty per cent are strongly positive. The actual clinical incidence of syphilis in these patients we believe to be much higher, a 75% incidence would be nearer the truth. In these 35,000 admissions in all services in eight years there have been eight cases of gastric syphilis in the medical wards. In 500 autopsies during the past three years definite demonstrable gastric lues has not been found. Despite the fact of the known

tendency to immunity of the gastro-intestinal tract to syphilis, it would seem that in this type of material it would be encountered more frequently. However, out of the 35,000 admissions in the eight year period we have records of only eight cases of gastric syphilis.

The findings in these cases in brief are as follows:—

*Case 1.* L. M., male, age 32. Chief complaint vomiting p.c. for one year, with weight loss of 54 pounds and history of penile sore. Physical examination, no palpable mass abdomen.

Laboratory data—Blood Wasserman strongly positive. Red cells 5,210,000, Whites 6,000.

Gastric analysis free HCl 20, total 55.

X-ray examination — Stomach shows spasm at pylorus suggestive of ulcer or syphilis.

Course—Remained in hospital 9 weeks. Antiluetic treatment.

Discharged improved. X-ray still shows prepyloric defect.

*Case 2.* W. J., male, age 45. Complaint of pain stomach p.c. vomiting and weight loss of 25 pounds.

Laboratory data—Blood, strongly positive Wasserman. Red cells 4,227,000, Whites 6700.

Gastric analysis—free HCl 24, total 59. X-Ray—Stomach narrowed and appearance that of malignancy.

Course—Remained in hospital 1 month. Antiluetic treatment.

Discharged improved. X-ray shows improvement in stomach deformity.

*Case 3.* C. H., male, age 63. Complaint pain in stomach, weakness, for 6 months. Loss of weight.

Gastric analysis—No free HCl.

Blood—Wasserman strongly positive. Red cells 3,690,000, Whites 9,800. Spinal fluid Wasserman negative. No palpable tumor.

X-Ray—Infiltrating defect along lesser curvature.

Course—After antiluetic treatment discharged from hospital, improved and X-ray shows lessening of stomach deformity.

*Case 4.* L. M., age 32, male. Complaint of pain epigastrium and vomiting. Weight loss of 54 pounds in 6 months. History of penile sore 9 years previously. No palpable tumor.

Laboratory data—Blood Wasserman, strongly positive. Red cells 4,000,000, Whites 5,200.

Gastric analysis free HCl 20, total 55.

X-Ray—Defect on lesser curvature stomach.

Course—After antiluetic treatment, no further pain. X-ray shows marked improvement in outline, which has returned to about normal.

*Case 5.* C. M., age 22. Chief complaint pain and vomiting for seven months. History of penile sore 3 years ago. Loss of 30 pounds in weight.

Laboratory data—Gastric analysis—no free HCl.

Blood—Wasserman strongly positive. Red cells 4,830,000. Whites 14,000.

X-ray shows no defect in gastric outline.

Course—Hospital 6 weeks and after antiluetic treatment, shows marked improvement and is able to retain food.

*Case 6.* W. N., male, age 20. Chief complaint pain in stomach, vomiting, loss of weight for 7 months. History of penile sore. No palpable masses in abdomen.

Laboratory data—Gastric analysis free HCl 35, total 38.

Occult Blood positive. Wasserman strongly positive. Red cells 3,830,000, Whites 7,300. Blood chemistry normal. Spinal fluid negative.

X-Ray—Marked spasm stomach and filling defects about pylorus.

Course—Hospital 4 weeks. Antiluetic treatment. Dismissed condition improved.

*Case 7.* A. S., male, age 25. Chief complaint, vomiting, pain, weakness. Loss of 30 pounds in weight. History of syphilis 3 years previously.

Laboratory data—Gastric analysis no free HCl.

Blood—Strongly positive. Wasserman. Red cells 1,900,000. Whites 7,700. Hgb. 50%. Blood chemistry normal.

Stool—Occult blood negative.

X-Ray—Stomach negative except for irregular duodenal cap.

Course—After three weeks antiluetic treatment, looks and feels better, and Hgb. has increased from 50 to 85%.

*Case 8.* W. M., male, age 27. Chief complaint vomiting, inability to retain food for 12 months. Penile sore 3 years ago. No palpable mass in abdomen.

Laboratory data—Gastric analysis, no HCl present. Stool positive for occult blood. Wasserman strongly positive. Hgb. 80%, red cells 4,590,000. Whites 9,000.

X-Ray—Stomach tubular, hour glass type. Pylorus gaping.

Course—Hospital 5 weeks. Antiluetic treatment. Relief of symptoms. Gain of 30 pounds in weight. Repeated X-rays, no change in gastric deformity. Absence of Hcl persists.

*Comment.* One notes that in this series of cases all are males. From the literature it would appear that the sex ratio is two males to one female.

The age incidence in this group is greatest between 20 and 30. The history of onset is from 2 months to 18 months. All of the series have a clinical history of syphilis. All have strongly positive Wasserman reactions. All have suggestive symptomatology. All show improvement after anti-luetic treatment.

*Symptomatology.* The chief clinical symptoms are—great weight loss, secondary anemia, epigastric pain and persistent vomiting with the inability to retain food.

*Physical Findings.* It is characteristic of gastric syphilis that palpation of the abdomen reveals no masses, although this may occur, of course. Epigastric tenderness is elicited. This is diffused and shows no localization.

*Laboratory data.* The blood usually shows a positive serology, although a negative serology may exist with definite clinical evidence of the disease. Low hemoglobin, low red cell count. Gastric analysis usually shows an absence of hydrochloric acid, which persists even after treatment. The stools may or may not show occult blood.

*Roentgenological Findings.* Evidence of infiltration of the gastric wall, obstruction, or of gaping pylorus occurs in this series, and in only one case was the stomach negative roentgenologically. The X-ray signs of gastric syphilis are:

- (1) A concentric, symmetrical defect of the gastric lumen.
- (2) The stomach appears high, and the lumen narrowed.
- (3) If the lesion is antral it appears in a narrowed tubular effect.
- (4) If the lesion is of the hour glass type, the isthmus of the hour glass is elongated and dumb-bell like.
- (5) The pylorus may be gaping, or less frequently obstructive.
- (6) Six hour residues are not found except in the obstructive type.
- (7) The technical point of differentiation from carcinoma lies in the fact that the syphilitic lesion is symmetrical while the carcinomatous is irregular and asymmetrical. Where both lesions are at the pylorus it may be impossible to differentiate.

Syphilis may involve the stomach in three ways, namely (1) A diffuse syphilitic gastritis. (2) Syphilitic ulcer. (3) Gummatous infiltration.

Perhaps the large infiltrating gummatous lesion is the one most frequently diagnosed. The consensus of



opinion is that in no sense is peptic ulcer etiologically related to syphilis, although this view is held by Parody. It should be remembered that syphilitics can develop peptic ulcer or carcinoma independent of constitutional syphilis and their treatment responds to non-specific measures. It is said that syphilis of the stomach occurs once to every one hundred other organic lesions such as ulcer or cancer. It is interesting to note that in only one case in the literature have spirochetes been demonstrated in the gastric lesion, that of the case of McNee, and the authenticity of this case has not been accepted by some recent writers.

*Treatment.* Antiluetic treatment produces marked improvement, the symptoms abate, weight increases, and the infiltrating gastric lesions regress, although in some cases X-ray shows the structural defects persists. Achylia which occurs frequently in the disease also persists after treatment. Achylia in syphilitics has been observed for some time.

It is to be remembered that syphilis may accompany an organic lesion and

that a general improvement under antiluetic treatment may occur, which may be misleading, and valuable time in operating on a malignancy may be lost.

In the management of a gastric hemorrhage of unknown origin, it has been brought out by some observers that the etiology may be syphilitic.

#### CONCLUSIONS

(1) Eight cases of gastric syphilis are tabulated occurring in an admission of 35,000 cases in a general teaching hospital.

(2) Comment is made that so few cases have occurred in such a large syphilitic material.

(3) Presenting symptoms in gastric syphilis are—pain, vomiting, loss of weight, Positive blood Wasserman, and characteristic X-ray findings.

(4) The attributing of all gastric symptoms to an existing constitutional syphilis is to be avoided, as they may be entirely independent thereof.

(5) In the investigation of chronic disease of the gastro-intestinal tract syphilis may be the etiologic factor.

## Observations of Heart Action Under Vagus Stimulation\*

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FOR some years the view has been held by observers of first rank that the right vagus is commonly more intimately associated with the sino-auricular node and its activities than is the left vagus. It has long been noted that the slowing of the heart as result of stimulation of the right vagus is usually more marked than is the slowing as result of stimulation of the left vagus. It is certainly also a matter of common observation that in any group of normal adults the individuals vary greatly one from another in their responses to vagus stimulations. Accumulated routine records of normal variations should throw suggestive light on the problems of abnormal variations, in that the differences between the normal and the abnormal may often be only those of degree.

With the foregoing thoughts in mind it occurred to the writer that a report of the differences in responses to right and to left vagus stimulations in a series of fifty adult males, with apparently normal hearts, might be of some clinical interest.

This report includes the routine observations of fifty men whose ages

ranged from 30 to 60 years, all being, at the time the observations were made, in fairly good general health. These records are chiefly those of the responses to stimulation of the right vagus and to like stimulation of the left vagus by digital pressure on the respective nerve and its neighboring structures within the corresponding carotid sheath, at the position in the neck where they were most readily accessible, this being near the level of the body of third cervical vertebra.

It should be borne in mind that these responses may not have been entirely due to the vagus stimulations alone, for the associated pressure on the carotid artery certainly did markedly diminish the arterial blood supply to the brain. It was regularly observed that for the period that the pressure on the carotid sheath was continued the radial pulse was notably decreased in volume and that immediately the pressure on the carotid sheath was released the radial pulse regained its former character.

It was something of a surprise to find that in this group the ages of the individuals were of little importance in the classification of their response to vagus stimulations. The younger men were not more responsive to the vagus

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stimulation tests than were the older men. As a matter of fact, the two men who showed the most marked pulse slowing with vagus stimulations were 43 years and 56 years of age respectively. These men were both quite self contained and showed no nervous or neurotic manifestations. Neither of them gave any history of cardiac trouble and neither had any other physical findings suggestive of cardiac abnormality except that one of them had a rather marked sinus tachycardia.

It was also observed that the men who had very definite respiratory sinus arrhythmia were not more apt to show marked pulse slowing from direct digital pressure on the vagi in the neck than were those men whose electrocardiograms gave no suggestion of respiratory sinus arrhythmia.

Of the 50 individuals of this group, five (10%) showed no responses at all in the rate or character of the pulse as

result of digital stimulation either of the right or of the left vagus; forty-four (88%) showed definite slowing of the pulse as result of the digital pressure and one (2%) showed a slightly increased pulse rate, from 54 to 60, with digital pressure, this increase being the same with pressure on the right as on the left vagus.

With fourteen (28%) of the individuals the pulse slowing on stimulation of the left vagus was equal to the slowing on stimulation of the right vagus; with three (6%) the slowing on stimulation of the left vagus was more marked than the slowing on stimulation of the right vagus and with twenty-seven (54%) the pulse slowing was more marked on stimulation of the right than on stimulation of the left vagus. It is of special interest that, of the three individuals who showed more response to stimulation of the left than to stimulation of the right vagus, the

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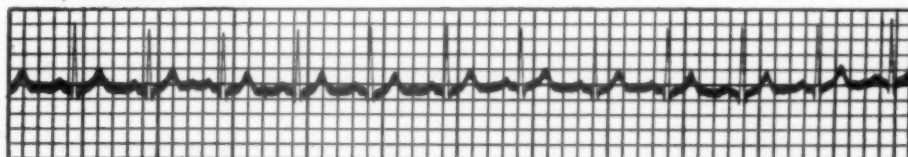


FIGURE 1. LEAD I.

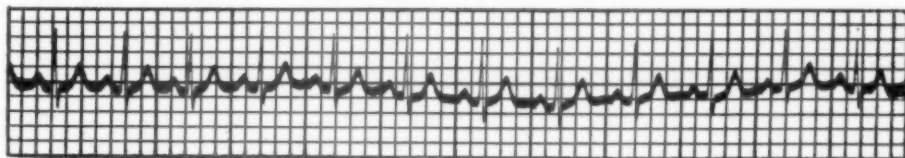


FIGURE 2. LEAD II.

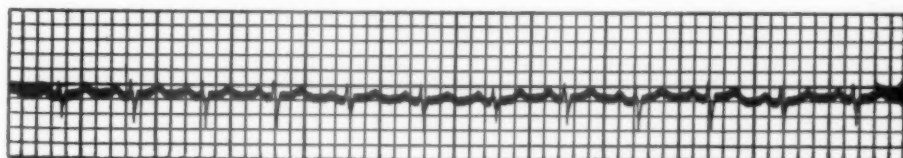


FIGURE 3. LEAD III.

one who showed the most marked response on left vagus stimulation was a man with congenital dextrocardia and apparently complete transposition of thoracic and abdominal viscera.

Electrocardiograms are here presented of the one man in this group of fifty who showed the most notable pulse slowing with vagus stimulations. These electrocardiograms are of a practicing physician, 43 years of age, who for a long time has been aware of his marked susceptibility to vagus stimulation. Figures 1, 2 and 3 are records of the 1st, 2nd and 3rd leads taken just before the vagus stimulation experiments were started. It will be observed that there is nothing remarkable in these except that the rate is rather rapid, 120, and that there is a very slight sinus arrhythmia which is of the respiratory type. Figure 4 was taken as the patient breathed very slowly and deeply and the record shows the respiratory sinus arrhythmia

to be slightly more evident. Steady and firm pressure was then made on both eyeballs, but the record is not here reproduced for the reason that no slowing of the pulse rate or other features of interest were shown. Figure 5 is the record as digital pressure was made on the left vagus. It will be observed that with pressure on the left vagus the pulse rate decreased at once from 120 to 75, but that there is otherwise very little change to be noted.

Figure 6 shows the sudden and very marked slowing as digital pressure was made on the right vagus, the period of heart stand-still between beats having been two full seconds. Except for a slight widening of the T, no notable changes in the complexes are observed at first. As the digital pressure was repeated, with only a few moments of intermissions, constantly varying records were produced, some of which are shown in Figures 7, 8 and 9. In Fig-

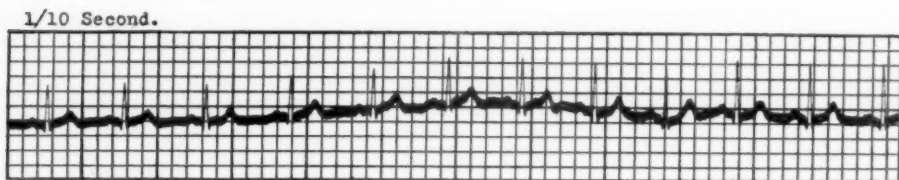


FIGURE 4. LEAD I.

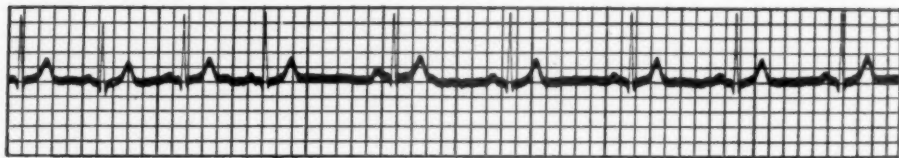


FIGURE 5. LEAD I.

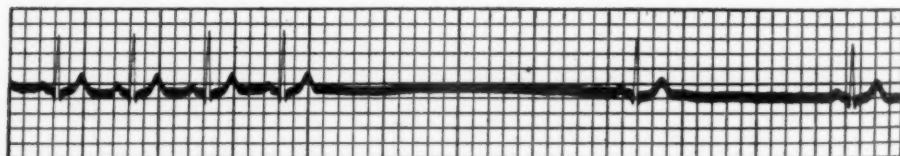


FIGURE 6. LEAD I.

ures 7 and 8 the pacemaker is seen to have shifted to various positions, and in Figure 9 the heart is seen to have stood still for approximately  $3\frac{3}{4}$  seconds, representing the period of 7 regular heart beats. Peculiarly the complexes which immediately followed the long pause are quite normal in character.

#### CAUTION

Due consideration for the comfort and safety of the subject should always be kept in mind. By careful and steady pressure with the ball (not the end) of the thumb unnecessary discomfort can be avoided. The physician who was the subject of the electrocardiograms here reproduced was apparently not at all annoyed by the experiences incident to the making of these records. With such interested and co-operative subjects the examiner may be strongly tempted to multiply and vary the routine tests. Here a serious word of caution should be sounded: *One should not attempt to*

*stimulate both vagi at the same time.* Sir Thomas Lewis states that harm has resulted from such an experiment.\*

#### CONCLUSIONS

1. There are evidently very great variations in the responses of normal individuals to vagus stimulations.
2. It is most difficult to determine just where to draw the line between the normal and the abnormal responses to vagus stimulations.
3. Of the fifty individuals observed twenty-seven showed more slowing of the pulse on stimulation of the right vagus and only three showed more slowing on stimulation of the left vagus, which seems to support the view that the right vagus commonly has more control over the sino-auricular node than has the left vagus.

\*LEWIS, SIR THOMAS: *The Mechanical and Graphic Registration of the Heart Beat*, 3rd Edition, 1925, p. 430.

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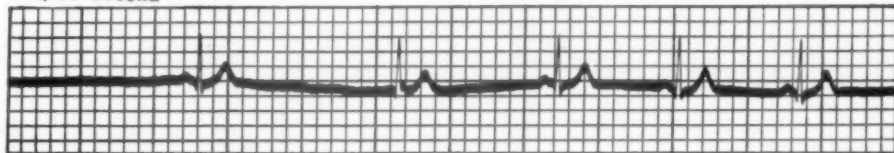


FIGURE 7. LEAD I.

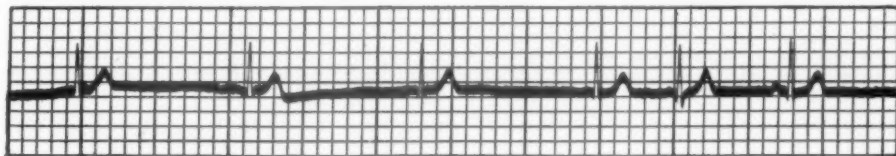


FIGURE 8. LEAD I.

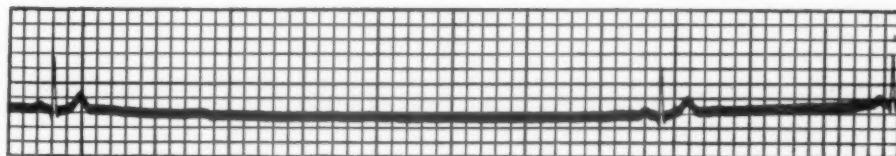


FIGURE 9. LEAD I.



## Editorials

GALEN  
130-1930.

This year marks the eighteen-hundredth anniversary of the birth of Galen who in his early thirties won such distinction as a practitioner in Rome that he became known as "Paradoxologus," the wonder-speaker, and "Paradoxopoeus," the wonder-worker. He was born in Pergamus in Mysia. He began the study of medicine at the age of seventeen, and in his twentieth year went to Smyrna in order to study anatomy under Pelops. He visited other Mediterranean schools, and finally went to Alexandria. In the course of his wanderings he studied anatomy under three of the pupils of Quintus, who was himself the pupil of Marinus. The latter had written a complete textbook on anatomy, which has been lost. Of this teacher Galen wrote that everything he described he had "touched with his own hands and seen with his own eyes." About 160 he went to Rome where he remained until 168, when he returned to his native city, but went back to Rome in 170. In Rome he had unparalleled success as a practitioner, curing Eudemus, a celebrated philosopher, and other noted persons, also incidentally, incurring the jealousy of his fellow practitioners. He finally became personal physician to the Roman Emperors from Marcus Aurelius to Septimus Severus. Galen was a born investigator. During his

early days in Rome he held public dissections of animals. He constantly studied, taught, criticized, observed, and investigated. He was one of the most versatile and accomplished writers of his age. It is said that he composed nearly 500 treatises on a great variety of subjects, including logic, ethics, and grammar. Of the works attributed to him, 83 are recognized as genuine, 19 are of doubtful authenticity, 45 are spurious, 19 are fragments, and 15 are notes on the writings of Hippocrates. He rewrote all of ancient medicine in the light of his own experience and observations. It is, however, not always possible to distinguish what was original with Galen, or what was known to the older anatomists. To the modern reader the works of Galen seem unsystematic, repetitious, and often inconsistent. He applied descriptive phrases rather than names to anatomical structures, and this habit makes his writings difficult and tedious. His style was, however, clear and animated. But within this great mass of writing, there is, however, a very complete account of the structure of the animal body. This knowledge was confined, by the circumstances of the times, to the dissection of animals, and this led later to great confusion which was cleared up by Vesalius. Galen was a thoroughly practical anatomist. He not only describes the organs, but gives ample



directions for their dissection and exposition. He appears to have been the first anatomist to attempt to discover the uses of organs by vivisection and experiments on living animals. In this way he determined the position and movements of the living heart. Through a series of experimental observations he demonstrated that section of the optic nerve caused blindness, and that section of the oculomotor nerve destroyed the motion of the eyeballs. Galen's osteology was the most perfect branch of anatomy of the ancients. In the branch of myology he appears to less advantage, though advancing this field of anatomical knowledge to greater perfection than any of his predecessors. His knowledge of the circulatory system was vitiated by the erroneous physiology of the period, yet presents some accurate observations showing his skill in dissection. He worked out a fairly well detailed account of the brain, and recognized seven pairs of cranial nerves. In his account of the thoracic and abdominal organs his descriptions are in general accurate. His description of the reproductive organs is brief and too much confused with physiological dogmas. The anatomical writings of Galen constitute a remarkable era in the history of anatomy. Through his diligence in dissection and accuracy of description, he gave the science a position of importance which it held for many centuries. He attained a position of universal authority in anatomy. He was read, quoted, and copied for thirteen hundred years. During this period his statements were never questioned, or tested by independent observation. His books were trans-

lated into Syriac and Arabic. There were no separate original books on anatomy in Arabic, but the encyclopedic works of Rhazes, Ali Abbas, and Avicenna, in the tenth and eleventh centuries, contain long chapters on anatomical subjects. These all had their origin from Aristotle and Galen. Galen's anatomy we know to have been derived from animal dissections. In the Arabic textbooks his anatomy was applied to man without question, hence during the Middle Ages was accepted as authoritative and final. By the middle of the thirteenth century, the Italian translators had Latinized Aristotle, much of Galen, and the majority of the Arabians. Chaucer's "Doctour of Phisik" knew well his "old Ypocras and Galien." The pre-Vesalian anatomists retained intact the Arabic Galen-traditions. These ruled supreme until Berengario at Bologna in the early sixteenth century first subjected the authority of Galen to critical examination, and denied the so-called middle ventricle of the heart and the multichambered uterus, and openly and frankly declared that he was confused by the discrepancy between some of Galen's descriptions and the actual anatomical findings in human bodies. In 1525 a complete edition of Galen in Latin was issued by the Aldine press. This publication permitted the true evaluation of the ancient knowledge. In the earlier years of his career Vesalius was a follower of Galen, but about 1540, being asked to assist in editing a complete Latin edition of Galen, he became greatly perplexed by the discrepancies between Galen's descriptions and the human body. During this year he happened to find a

bony process, the anapophysis, in a monkey's vertebra, which had been described by Galen, but which he himself could not find in man. The truth flashed upon Vesalius—Galen had written his descriptions from animals, and not from the human body. Thus was the Galenic anatomic tradition of fourteen centuries broken, and the foundation for the modern science of anatomy securely laid. In his theory of medicine and medical practice, Galen was a follower of the Hippocratic doctrine of humors. This he developed with great but fatal ingenuity into the theory of normal temperaments and the abnormal distempers. The latter were not diseases but were the occasions of disease. Equal importance attached to dyscrasias or faulty mixtures of the blood. All diseases were produced through the combination of these morbid predispositions with the action of harmful influences from without. On this system he explained all diseases, giving to every phenomenon a name, and having a solution for every problem. In this fine-spun philosophy he departed farthest from scientific principles. He based his use of drugs upon the same theories of hot, cold, moist, and dry, as in the human body; and on the principle of curing by contraries, the use of one or the other was indicated. Galen's theoretical explanations and dogmatic expositions appealed to the indolent mental habits of succeeding ages. His system gained in favor during the middle ages, assuming a position of autocratic influence throughout Europe until the development of modern science in the seventeenth and eighteenth centuries.

Out of Galen arose the greater part of modern European medicine.

*THE INFLUENCE OF SUPRA-  
RENALIN (EPINEPHRIN) ON  
THE GROWTH OF CARCI-  
NOMA AND SARCOMA  
IN ANIMALS.*

Since the isolation by Abel of the active principle of the suprarenal gland in 1897, this substance has been widely used as a vaso-constrictor and hemostatic agent. These properties naturally suggested that the active principle, epinephrin, might have a destructive effect upon certain types of neoplasm. In 1910, Reicher reported that the injection of adrenalin in the neighborhood of rat sarcoma and mouse carcinoma caused a central necrosis and subsequent destruction of these tumors. Uhlenhuth, Haendel, and Steffenhagen found that the local application of adrenalin had very little therapeutic effect on rat sarcoma. On the other hand, Lumsden and Stephens reported that the injection of adrenalin and anti-Jensen rat sarcoma serum into and around the Jensen rat sarcoma caused regression of the tumor and produced active immunity in the animal. At the International Physiological Congress in Boston, in 1929, Sokoloff showed that the intra-tumor injection of a mixture which contained adrenalin, pyrrol blue, and ferric chloride, produced local regression of transplanted tumors in rats and mice. Sugiura and Benedict, about six years ago, carried out an extensive investigation on the effects of epinephrin on transplanted animal tumors. Although they observed regression and apparent destruction of the transplanted tumors

in a large percentage of the transplanted tumors, they were pessimistic as to the application of this hormone in the treatment of human cancer. In the *Journal of Cancer Research*, October, 1930, they report these earlier experiments, and at the same time answer the question as to the possible value of epinephrin in the treatment of malignant neoplasms in the human being. They investigated the toxic action of suprarenalin on the Flexner-Jobling rat carcinoma and the Rous chicken sarcoma in three different ways: namely, 1, injection directly into and around the tumor; 2, injection subcutaneously at a point away from the tumor; and 3, *in vitro*. They found as a result of their work that the development of small tumors in animals is completely inhibited by repeated intramural injections of suprarenalin, while large tumors are seldom beneficially affected by repeated injections. The repeated subcutaneous injection of suprarenalin at a remote point does not affect the growth of rat carcinoma and chicken

sarcoma. *In vitro* experiments showed that the proliferating capacity of the Flexner-Jobling rat carcinoma was partially destroyed by suprarenalin, but the Rous chicken sarcoma was unaffected as respects its growth after implantation. Hence, these investigators conclude that any possible value of suprarenalin (epinephrin) for the treatment of cancer is limited to local application. Recently Coffey and Humber have reported that the injection of an extract of sheep suprarenal cortex produced changes in human cancer tissue. This has led to an extensive advertising of this substance by the public press as a cancer cure. The work quoted above of Sugiura and Benedict shows that there is no scientific foundation for a belief in any specific action of adrenal cortex upon neoplasms, and that any possible change produced in them by the injection of such is wholly of a local destructive nature. A thousand other substances can be found that will produce a similar effect.

## Abstracts

*The Etiology of Erythema Nodosum in Children. Its Relation to Early Tuberculous Infection.* By Lloyd B. Dickey (Amer. Jour. of Med. Sc., October, 1930).

Observations of nine cases are reported. Three of these were in boys, aged two and a half, two and a half, and fourteen years respectively. Six occurred in girls, aged three, three and a half, nine, ten, ten, and twelve years respectively. In those cases in which previous tuberculin tests had been done, all were negative except in two cases, although at the time of the appearance of the lesions of erythema nodosum, or shortly after, all tuberculin tests were strongly positive with induration, tenderness, and erythema, which in most cases simulated closely the nodular lesions over the tibiae. In one instance the nodules appeared about twenty-four hours after the introduction of tuberculin into the skin. In only two cases in this series was a history of exposure to tuberculosis elicited despite the fact that all skin tests were positive. The author concludes that erythema nodosum may occur in non-tuberculous individuals or in those infected with the tubercle bacillus. The great majority of cases of erythema nodosum in children are associated with a tuberculous infection, and most of the infections are initial and recent. Most children who have erythema nodosum exhibit marked hypersensitivity to tuberculin given intracutaneously. There may be associated, in addition to the tuberculosis infection, other conditions which possibly influence the hypersensitivity to tuberculin. In many cases of erythema nodosum in children epituberculous lesions in the pulmonary parenchyma can be demonstrated by roentgenograms of the chest. In the series reported, none of the individuals observed was known to have a very active tuberculous lesion of the lung. The lesions of erythema nodosum, with epituberculous lesions and the positive skin

tuberculin reactions are similar histologically. As erythema nodosum is usually associated in children with early tuberculous infections; proper treatment for the latter condition gives a favorable prognosis as far as tuberculosis is concerned.

*Gout in a Five Weeks Old Infant. An Important Observation with Reference to the Problem of Gout.* By E. Mayer von Schopf (Klin. Wchnschr., November 15, 1930).

Schopf reports a study on a unique case of gout, the youngest case on record. The literature records as the youngest case previously observed, that of a boy of four years, who had a history of symptoms for two and half years. The present case was that of a male infant five and a half weeks old, whose parents were young and healthy. There were two healthy sisters, one and three years old. The paternal grandfather had had swellings on his hands which disappeared under massage. The great-grandfather had died of dropsy. No other history of hereditary taint could be elicited. There was no history of diabetes, obesity, rheumatic affection, or of stone in the family. The father was a laborer. The living conditions were good. Birth was normal, and the child active and lively. It took the breast readily, but vomited after almost every meal. Its stools were increased and green. In the third week it developed an increasing restlessness, and the mother noticed that hard thickenings appeared upon the back of the hands, and that the fingers were stiff. There was no fever. Because of the vomiting the child was brought to the clinic with the suspicion of a pyloro-spasm. Examination showed no signs of this condition. No pathological findings were discoverable in either thorax or abdomen. Examination of nervous system was negative. The backs

of the hands showed bean-sized tumors of hard consistency on the extensor tendons of the third and fourth fingers. The skin over the tumors was pale, movable, and without signs of reaction; apparently not painful on pressure. The stools were increased, with small amount of mucus. Albumin in urine. Bile pigment not increased. Sediment of urates. Blood Wassermann was negative. The x-ray examination of the hands showed normal bone and joint structure; the tumors gave no shadows. The differential diagnosis was multiple abscesses? Congenital neoplasm with metastases? Tendovaginitis fibrinosa? On the fifth day the child developed signs of bronchopneumonia, with a leucocytosis of 34,000. On the third day new tumors were observed on the left hand and on the foot. Puncture of the latter led to the discharge of a snow-white pultaceous material, which microscopically showed needle-shaped crystals, arranged in bundles, and also amorphous masses. No bacteria were found. Cultures were sterile. Death took place on the night following the sixth day. The autopsy showed marked cachexia, involution of thymus, paravertebral bronchopneumonia of both lungs. Slight catarrhal colitis. The chief pathological diagnosis was gout. Numerous swellings, firm in consistency were found on the back of both hands. The overlying skin showed no reaction, and was pale and movable. The tumors were well circumscribed, and varied in size from a pea to a plum. A chalky pasty material was found in the subcutaneous tissue, in the musculature and on the palmar aponeurosis. The wrist joint and the articulations of the wrist-bones were covered with white masses. The joints of the lower extremities showed no such deposits. Chemical examination showed this material to be made up of urates. Microscopically it consisted chiefly of needle-shaped crystals, with other forms of crystals of uric acid. Both kidneys were enlarged and swollen. Through the capsule the surface showed an appearance as if covered with grits. The capsule was somewhat adherent. The surface was very pale, and strewn with white, slightly elevated granules. The cut section showed medullary

pyramids and cortex to be infiltrated with white granules and stripes of a pultaceous material. In the pelvis a few white crumbling calculi were found. Microscopical examination of the joints and bones of the hands showed an abundant, chiefly amorphous, deposit of urates, with typical needle and columnar crystals. The bone, cartilage, periosteum, and synovial membrane appeared to be unchanged, and inflammatory reaction was wholly absent. The kidneys showed on microscopic examination marked crystalline deposits. The glomeruli showed no changes. The epithelium of the convoluted tubules was well differentiated; many of the tubules contained hyaline casts. Between the collecting tubules of the medulla there was a proliferation of small spindle-cell fascicular connective tissue. Sudan III gave a light brown color to the epithelium, but there was no marked fatty change. The crystalline deposits for the greater part lay between the tubules of the cortex. They consisted chiefly of fine needles, occasionally columnar-shaped bundles, with radial arrangement. Many of them had a capsule of spindle cells about them, containing foreign-body giant cells. Occasional leucocytes are found between the crystals. In the medullary portion of the kidney part of the crystalline masses lay free, others were found in the dilated straight tubules. Also needle and bundle-shaped collection of crystals were found without epithelial or connective-tissue capsule. The small arteries and arterioles showed no change. The kidney was interpreted as a gouty contracted kidney, similar to that in the adult gouty patient. The deposits of crystals were of extraordinary extent and degree, and the cortex was especially involved in the process. There was but little lime-salt present. The crystalline deposits were predominantly interstitial, but occurred also within the tubules. There was a diffuse proliferation of the stroma. Severe interstitial changes were associated with the urate deposits. These kidneys were differentiated from those of the uric acid infarct of the newborn, but the fact that the deposits were white and not yellow, and in the latter con-



dition the urates are wholly in the tubules and not in the interstitial tissue. Chemically the crystals in this case were monosodiumurate, instead of ammoniumurate as in uric-acid infarction. Moreover, these youngest gouty kidneys show chronic inflammation and contraction. In conclusion: This is the youngest case of gout on record. The intensity and extent of the uric acid deposits are very great. The development of tophi took place in very short time. The histologic appearance of these show no evidence of either primary or secondary inflammation. The bones showed no changes. There is no explanation of the cause of the retention of uric acid and its deposit in the tissues. Exogenous factors are completely ruled out. The constitutional pathologic factor is not prominent. The kidneys are true gouty contracted kidneys with abundant deposits of urates in the interstitial tissues. Tissue necroses were not found.

*Bechterew's Disease.* By von Ehrlich (Arbeit. u. Gesundh., Berlin, R. Hobling, 1930).

The symptom-complex described by Bechterew, Strümpell, and Pierre-Marie is not a disease entity, but is the sequel of an infectious disease. The symptoms appear in the vertebral column only under certain predisposing conditions. Rheumatism plays the chief rôle. Trauma and gonorrhea alone are not responsible. Skeletal anomalies and bad living conditions are important predisposing factors. Not only are the small joints involved, but also the vertebral bodies, disks, and ligaments. The pain is caused by pressure upon the nerves by over-filled veins, and by inflammatory changes in the nerve sheaths. The affection is of an inflammatory nature; after its healing, changes can develop which pathologically and roentgenologically show the picture of an arthrosis. Without a roentgenologic examination, the diagnosis of Bechterew's disease cannot be made. The treatment is chiefly the use of a supporting corset. Labor should not be too hastily resumed. Gymnastics and massage should be directed. From the standpoint of pathologic anatomy the fully developed symptom-complex can be

designated a spondylarthrosis ankylopoetica. The early stage is one of spondylarthritidis infectiosa.

*Endocardial Pockets.* By Otto Saphir. (Amer. Jour. of Pathology, November, 1930, p. 733).

In two cases of subacute bacterial endocarditis of the aortic and mitral valves with insufficiency of the aortic valve, endocardial pockets with openings toward the aorta were found on the interventricular septum of the left ventricle. The initial lesion which brought about the pocket formation was a circumscribed parietal endocarditis. The continuous regurgitation formed the pockets secondarily. In one case of rheumatic endocarditis of the mitral valve with insufficiency of this valve, endocardial pockets were present in the left auricle. These pockets were open toward the mitral valve. They also were primarily inflammatory in origin and formed secondarily after the insufficiency of the mitral valve had been established. In two cases of syphilitic involvement of the aortic valve with insufficiency of this valve, endocardial pockets open toward the aorta were found. These pockets were caused primarily by the mechanical irritation of the regurgitating blood columns. Two cases of syphilitic involvement of the aortic valve with insufficiency of this valve and marked stenosis of the conus arteriosus sinister, and one case of rheumatic endocarditis of the aortic valve with stenosis of its orifice, showed endocardial pockets in the interventricular surface of the left ventricle. These pockets were open toward the apex of the heart. They were brought about by the mechanical irritation of the systolic blood stream acting as trauma upon the endocardium in the region of the stenosed portions. Diastolic endocardial pockets are evidence in favor of the view of actual regurgitation of blood volume. The nomenclature of "diastolic pockets" referring to those open toward the aorta, and "systolic pockets" referring to those open toward the apex (Kraso) is justified. Endocardial pockets cannot be regarded as manifestations of functional adaptation.



*The Relation Between Cardiac Weakness and Angina Pectoris.* By H. Kohn (Deut. Med. Wchschr., September, 1930).

Kohn does not believe that either cardiac weakness or overwork of the heart predisposes to angina pectoris. Cardiac weakness, may, however, develop during or after an attack of angina. He is inclined to believe that spasm of the coronary artery is the etiologic factor in angina pectoris. This view has an important therapeutic application. Those who hold the view that cardiac weakness is the underlying cause endorse the use of cardiac stimulants for this condition. If coronary spasm is the real cause, stimulants, such as digitalis and strophanthine are more harmful than helpful, because they cause stenosis of the coronary arteries and thus aggravate the condition instead of improving it. Therefore, in place of these stimulants, nitrites should be given for their antispasmodic effect. If objection is raised against the nitrites because of their habit-forming effects, papaverine or theophylline may be administered with or without sugar solution. Atropine may also be used for its antispasmodic effect. In cases of total occlusion of the coronary arteries, caffeine and camphor may be administered. After an attack rest in bed is necessary, and digitalis may be given for the cardiac weakness. The recurrent pain that accompanies medication with digitalis may be prevented by the use of an antispasmodic in conjunction with the digitalis.

*Multiple Gummas of Heart in New Born.*

By John W. Williams (Amer. Jour. of Pathology, Sept., 1930, p. 573).

Williams reports the case of a full term negro female infant, aged 3 hours, in whose heart multiple grayish nodules were found. These were firm, well demarcated, and showed a small central area of softening. Microscopically they consisted of shrunken muscle fibers with varying amounts of a mucoid and vacuolated substance separating the muscle fibers. This substance has the appearance of debris and contains bits of striated muscle fiber, lymphocytes, plasma cells, monocytes, and polymorphonuclear leucocytes, giving the impression that muscle tissue which might once have been

present had been dissolved, and its place partially filled with these cells. Other areas of muscle showed considerable fatty change. Around the small arterioles there were infiltrations of plasma cells and lymphocytes. Staining for spirochetes showed the presence of enormous numbers. Microscopic examination of the other organs showed no evidence of syphilitic lesions. The mother's Wassermann was strongly positive. The pathology of these nodular lesions was identical with that described by Warthin under the term "myxogumma". The lesion does not appear to be a true gumma, and the author suggests the use of the terms syphilitic cellulitis and fulminant syphilitic myositis as descriptive of the lesion, since it is characterized by muscle destruction and infiltration with lymphocytes, polymorphonuclear leucocytes, monocytes, and plasma cells.

*Metastasizing "Carcinoid" Tumor of Jejunum.* By István Gáspár (Amer. Jour. of Path., Sept., 1930, u. 515).

A case is reported of multiple carcinoid tumors of the jejunum, one of which caused intestinal obstruction, with metastases in the mesentery and liver. Histological examination revealed the picture of typical carcinoid tumors. Serial sections definitely indicate that at least two of the tumors originated in the crypts of Lieberkühn. Positive silver impregnation confirms Masson's contention that the origin of carcinoid tumors is in the Nicholas-Kulchitzky-Masson cells in the glands of Lieberkühn. It is apparent that carcinoid tumors may occasionally assume clinical importance. Metastasizing carcinoids of the small intestine have been described by Ransom, Versé, and Schaffer.

*The Present Status of Streptococcus Biologic Products in the Prevention and Treatment of Scarlet Fever.* By M. V. Veldee (Pub. Health Rep., August 8, 1930).

In the Conference of Health Officers and the United States Public Health Service in 1926, it was the general opinion that the intradermal reaction to scarlet-fever streptococcus toxin is a fairly dependable measure

of the susceptibility of the individual tested. The majority of the individuals giving a positive reaction can be effectively immunized by the proper use of scarlet-fever streptococcus toxin. The use of scarlet-fever streptococcus antitoxin, either for passive immunization, or for the treatment of the individual with scarlet-fever, is not yet founded on sufficient clinical data to permit a mature opinion as to the efficacy of this form of treatment. The results of an immense amount of research work have been reported since the 1926 conference, yet there seems to be little reason to alter the opinions just mentioned. Agreement is fairly general that scarlet fever streptococcus toxin has found a definite field of usefulness in the active immunization of persons

susceptible to scarlet fever. However, agreement has not been reached as to the number of injections or the total dose of toxin required for the production of immunity. The time has not yet arrived for the proper evolution of scarlet-fever streptococcus antitoxin in the treatment of scarlet-fever. We are still in need of very closely controlled clinical demonstrations of the therapeutic value of such antiserum. There are certain shortcomings which need correction before the health officer can push the use of these new products in the prophylaxis and treatment of scarlet-fever. In order to attain general acceptance and usage, we must have a product which will require fewer doses and cause less reaction.

## Reviews

*A System of Clinical Medicine. Dealing with the Diagnosis, Prognosis, and Treatment of Disease. For Students and Practitioners.* By THOMAS DIXON SOVILL, M.D., London. Eighth edition. 1019 pages. 167 figures, 4 plates in color. William Wood and Company, New York, 1930. Price in cloth, \$10.00.

This book approaches disease from the standpoint of symptomatology. In this new edition every page of the book has been carefully revised. The chapters on Diseases of the Lungs and Liver, and the sections on the Pancreas, Mental Diseases, Urinary Examinations, Clinical Bacteriology, and Serum Therapy, have been completely recast. Much of the chapters on Debility and the Nervous System has been rewritten. Much new material has been added, and the chapters dealing with the specialties have been revised by the experts who wrote them. The writer is not in sympathy with the plan of this book. It is too one-sided and narrow in its outlook and method. It is woefully deficient in etiology, pathology, and the general natural history of disease. One might just as well have a card-catalogue of symptoms and treat his patients accordingly. The material has not been brought up-to-date, and much of it is antiquated. The plan is bad; no good textbook of medicine can be written by following such. Various typographical errors occur, as Tularemia is indexed for p. 546 instead of 556. This is a book which the student of medicine is advised not to purchase.

*Clio Medica. A Series of Primers on the History of Medicine.* Edited by E. B. Krumbhaar, M.D., Professor of Pathology, University of Pennsylvania. Published by Paul B. Hoeber, New York. Price in cloth, \$1.50 per volume.

This series of small handbooks on the history of medicine aims at presenting in a con-

cise and readable form special phases of the development and evolution of the art and science of medicine. The presentation of the history of medicine in one volume of necessity makes of that volume a book so large that its size discourages approach by any reader. Further, the chronological method, so universally followed in the comprehensive general histories of medicine, makes a more or less disconnected story of the history of the individual branches of medicine, so that any reader interested in the history of such branches, must hew his way through the mass of general material, only to find after all his labor, a disconnected and incomplete presentation of the subject. It is to obviate such difficulties that the plan of issuing a number of small primers concerned with different fields of medicine, presenting the history of such in the form of a connected tale was adopted. These books are of coat-pocket size, and can be easily carried about until an opportunity presents itself for reading. To the busy physician or student, this feature of this edition should make an especial appeal. The presence of a small volume at hand is a great saver of time, which on motor-car or railway train could be easily lost or wasted. The subject of medical history, treated in subdivisions in this way, lends itself particularly to such utilization of spare time. It is extraordinary how much knowledge of the history of medicine can be acquired in this way, almost casually or incidentally, without one's being aware of any effort expended in the process. Such methods have always been utilized and employed by the true student. He who seeks culture will find it, and often the exigencies of a too-busy life permit only this method of time-saving study and reading. It is a method that we should like to see extended to every member of the profession. It would be trite to dilate upon the advantages

of reading good things; but it may be pertinent to call attention to the possibilities of these little volumes in helping one to acquire a cultural knowledge of the history of medicine. And then the extraordinary low price at which this series is offered puts it in the reach of every one, even the hard-up medical student! The latter could afford to buy a volume every other three months or so, until finally his set is complete. And what an opportunity is here offered to one who is looking for an appropriate gift to present to medical man or student. At this season of the year such a hint is timely. The volumes of this series are written by well-known authorities in their respective fields, and each volume aims to tell the story of the evolution of some individualized phase of medicine in a compact, complete, and convincing form. Four volumes of the series have already appeared: 1, *The Beginnings: Egypt and Assyria*, by Warren R. Dawson; 2, *Medicine in the British Isles*, by Sir D'Arcy Power; *Anatomy*, by George W. Corner; and *Internal Medicine* by Sir Humphry Rolleston. Those in preparation are: *Physiology*, by John Fulton; *Pathology*, by A. S. Warthin; *Ophthalmology*, by Burton Chance; *Italian Medicine*, by Arturo Castiglioni; *Medieval Medicine*, by David Riesman; *Psychiatry*, by Charles W. Burr; and *Pediatrics*, by Isaac A. Abt. Other volumes are promised by editor and publisher, as these are published.

*The Beginnings: Egypt and Assyria.* By WARREN W. DAWSON, F. R. S. B., Fellow of the Royal Society of Medicine, of the Society of Antiquaries of Scotland, and of the Royal Anthropological Institute of Great Britain and Ireland. 86 pages.

The earliest medical documents in the world have come down to us from Egypt and Assyria. It is logical that a consideration of these should form the starting point of the study of medical history, and that an account of them should precede the volumes dealing with the medical progress of later times and other lands. The physical conditions of the Valley of the Nile have preserved for us the records of the most ancient intellectual activities. The

Egyptian custom of mummifying the dead influenced greatly the growth of medical knowledge; although embalming was a religious rite and not medical, it afforded opportunities for the acquisition of anatomy, and overcame the popular prejudice against the opening of the dead body, so that Greek anatomists were enabled to carry out a systematic dissection in Alexandria and elsewhere in Egypt. Three thousand years before the birth of Christ a definite effort developed on the Banks of the Nile to cope with the problems of life and death. Both embalmer and physician were concerned in devising means of protecting the individual against the supernatural dangers threatening his existence. The magical procedures used in both cases had the same object in view, the giving of life which death and disease threatened. The endeavor to prolong and protect life and to avert extinction was the human motive out of which the science of medicine developed. The embalmer preserved the physical body, the magician infused into it the vital substance hostile to disease and essential to the continuance of existence. The Egyptian customs first made anatomical dissections possible. In this way Egypt led the way to facilities for the advancement of knowledge and research which could not otherwise have existed. Because of this the debt of civilization to Egypt is incalculable.

*Medicine in the British Isles.* By SIR D'ARCY POWER, K.B.E., F.R.C.S., Eng., Honorary Librarian at the Royal College of Surgeons of England; Consulting Surgeon, St. Bartholomew's Hospital, London. 84 pages.

The history of medicine in the British Isles is largely a history of its medical corporations, which from early times have exercised an influence for good upon medical education and medical practice because their ethical standard has always been high. There is practically no knowledge about the practice of medicine in the British Isles until some years after the Norman Conquest. Saxon medicine, as far as is known, consisted chiefly of charms and spells with potions and local applications made from various herbs, many of which are still in

common use among the people. No one in Saxon times seems to have devoted himself entirely to medicine as a profession; the doctors were called leeches; and in every village there were persons who were thought to possess a special power, God-given or by inheritance, of curing disease. The earliest records in Scotland and Ireland show that medicine was a hereditary occupation. Medicine became a profession after the Norman Conquest, though there does not seem to have been any systematic teaching until about 1423. Medicine was at this time almost entirely in the hands of the Church, although there were undoubtedly a few lay physicians in the large towns. Little is known about the physicians. For the most part medicine was subordinate to their clerical duties. Surgery was carried on by laymen, of whom there were two classes: surgeons proper, or as they would be called now, consulting surgeons; and members of the Barbers Company, the general practitioners who attended the minor injuries of the people. The consulting surgeons existed only in London where they formed a small corporate body known as "The Fellowship of Surgeons". Their members varied from time to time from six to seventeen. They did not teach, and had no apprentices. In time of war they followed this or that leader, and flourished accordingly. The Guild of Barbers stayed at home, took apprentices and thrived. In 1462 the religious element had disappeared largely and the Guild became a company with exclusive rights and privileges. As early as 1423 an attempt was made to establish a joint college of Medicine and Surgery, but owing to the war on the continent, the surgeons trooped away, and that appeared to be the end of the matter. Throughout the 15th century the physicians remained unincorporated. In 1518 they obtained a charter creating a College of Physicians in London. In 1540 the Barbers Company and the Fellowship of Surgeons were incorporated into a single company called "The United Company or Barbers and Surgeons." This lasted until 1745 when it was dissolved, the barbers separated, and the surgeons continued as the "Surgeons Company" which undertook the

teaching of surgery, but fell into disrepute, and the company was dissolved in 1796. Four years later the College of Surgeons was founded by charter and remains today as "The Royal College of Surgeons". "The Society of Apothecaries" was incorporated in 1617. The incorporation of the profession in Scotland and Ireland followed the same lines as in England. The Royal College of Surgeons in Scotland was incorporated in 1778; the Royal College of Physicians in Edinburgh obtained its charter in 1670. The history of the great English hospitals is given, as is also the history of medical education and nursing. Two chapters on the medical societies and the masters of British medicine close this well-written and interesting condensation of the history of medicine in the British Isles.

*Anatomy.* By GEORGE W. CORNER, M. D., Professor of Anatomy in the University of Rochester. 8 illustrations, 82 pages.

This volume reviews the development and evolution of the science of anatomy in six chapters dealing with the following subjects: Chapter I, The Greeks; Galen and Galenic Tradition; Chapter II, The Middle Ages; III, Modern Anatomy; IV, Histology, Embryology, Neurology; V, Current Trends in Anatomy. The actual recording of anatomical knowledge began in very early times, for the oldest written records of the papyri are compiled from earlier books and repeat a traditional lore which had already been codified, much in the style of a modern compend. The first definite investigation of anatomical questions of which we have record is in the sixth century B.C., when Alcmaeon of Croton is said to have dissected animals, to have discovered the optic nerve and the Eustachian tubes, and recognized the prime importance of the brain. The anatomy of the Hippocratic collection is trivial and theoretical. Aristotle and his school did not directly influence human anatomy. In spite of his errors, however, he started a movement in Athens in the study of mammalian and human anatomy which did not die out. It was in Alexandria that for the first time anatomy was developed into a distinct branch of science. The books of Herophilus and



Erasistratus have disappeared but through Galen we have knowledge of their anatomical discoveries. After these two leaders there seem to have been no important investigations carried on in Alexandria, but the school remained the chief center of anatomical teaching for nearly 500 years. Galen advised his pupils to go there for study. Galen revived the spirit of investigative anatomy. Of his preserved work there is enough anatomy to make a volume half as large as Gray's "Anatomy". He described the skeleton very well, and was especially interested in the muscles. After him there was no independent investigation of the medical sciences in the whole Roman Empire. Galen's writing became the universal authority, and were read, quoted, and copied, as supreme, for thirteen hundred years, never questioned, and scarcely even tested by fresh observation. By the Arabian school which followed, Galen's anatomy was applied to man without a question, and was accepted as authoritative and final. During the Dark Ages, Anatomy seems to have disappeared completely. Not until the 13th century was dissection revived, and the way paved for the great anatomical advances of the next four centuries. Mondino was the first teacher known to have taught anatomy from the human cadaver in Europe. At those early human dissections there was no thought of independent critical investigation; the business of the professor was of course simply to verify and illustrate the Galenic lore. Berengario was the first independent investigation of modern times, and his two text books were the first to contain pictures systematically illustrating the text. Through three hundred years of slow development, anatomy had been gradually progressing in both knowledge and technique. It remained for Vesalius to take up the torch lighted by these pre-Vesalian anatomists and to raise anatomy to the position of a pure science. The publication of his "Fabrica corporis humani" marked the death of tradition and authority and the birth of intellectual freedom. The foundation stones of modern anatomical observation and investigation were thus securely placed, and with-

in a generation there were anatomists all over Europe who had learned from Vesalius to dissect and analyze the human body for themselves. Then followed the full fruition of the Age of Anatomy during the 17th century, with the great names of Harvey, and other masters who have left their marks upon the terminology of anatomical science. The story of modern anatomy now follows, with the development of histology, embryology, and neurology, told in a concentrated but interesting form. Now when almost everything has been seen that can be discovered in the cadaver with knife and microscope, the anatomist has received new struments and new methods of investigation. The older static anatomy is moving toward a functional viewpoint. The dissecting room will always be the starting point of the anatomist's work; but the problems of human structure demand for their solution the utilization of all the resources of science.

*Internal Medicine.* By SIR HUMPHRY ROLLESTON, Bart., G.C.V.O., K.C.B., M.D., Hon. D.Sc., D.C.L., LL.D., Regius Professor of Physic in the University of Cambridge, England. 92 pages.

The long story of the development of internal medicine is detailed through the centuries by Rolleston in the following chapters: I, Ancient Medicine; II, Greek Medicine; III, Greek Medicine in Rome; IV, Links between Greek and Modern Medicine; V, the Renaissance and the Seventeenth Century; VI, The Nineteenth Century. This is the least satisfactory of the four volumes published to date. Much of it consists only of a catalogue of names and dates. It is too conventionally treated to hold the interest of the reader. It seems to the writer that in a medical primer of this kind, it is much better to consider the evolution of the subject from the philosophic side rather than attempt a recital of all the individuals concerned in that evolution. Rolleston's book lacks interest and readability, because he has followed the conventional medical history treatment of his theme. It is only a condensed manual of medical history, and lacks the interest of individual literary flavor. Moreover, his choice of American internists for mention



in his book strikes one as very peculiar, and inadequate. Better to have left out all mention of American medicine than to represent it by the poor choice given. It may be urged in excuse of the fact that this book falls so far behind the other three in its performance, that the problem of showing a spiritual or intellectual development of Internal Medicine is perhaps a larger undertaking than in the case of the others.

In conclusion, it may be said that the *Clio Medica* represents an undertaking well conceived and planned, and of great value to medical students and physicians who have cultural bents. In these little books they will find a maximum of intellectual food at a minimum cost and trouble. They can be recommended most highly for the purposes for which they are intended.

## College News Notes

### THE FORTHCOMING CLINICAL SESSION IN BALTIMORE

The Fifteenth Annual Clinical Session of the American College of Physicians will convene in the City of Baltimore during the week of March 23, 1931. The privilege of meeting in this city was made possible through the cordial invitation of the Johns Hopkins University School of Medicine, the University of Maryland School of Medicine, the Medical and Chirurgical Faculty of the State of Maryland, the Baltimore City Medical Society, and the further coöperative interest manifested by the various Baltimore hospitals and civic societies. It is to be hoped that this meeting will at least equal in excellence those which have been produced in recent years in other cities; and it is the belief that all who will attend this meeting will find ample in the way of clinical, laboratory, research and historical interest, well to repay them for the time spent in making the journey.

Local conditions, as well as medical and hospital facilities, greatly affect and alter the construction of programs; and at this writing the actual titles of papers and clinics to be presented, by whom, when and where, are far from being in a completed and final state. Moreover, it is possible that for reasons, both of economy and others, the former precedent of issuing a preliminary program may not be lived up to, though this also is not final. In any event, the final draft of the program of the Baltimore Session will be in the hands of each member in ample time for him to peruse it carefully and make his selections well in advance of the actual time of the meeting. Nevertheless, it has seemed wise to issue a preliminary statement about the meeting in the form of a printed article, outlining thus nearly four months in advance the general scope and construction of the Clinical Week.

At the risk of repetition, the following points with reference to the meeting will bear repetition:

(1) *Time and Place:* March 23-27, 1931, in Baltimore, Maryland.

(2) *Hotel Headquarters* will be at the Lord Baltimore Hotel; and it is important at this point to emphasize the wisdom of making early hotel reservations, whether they be at Hotel Headquarters or at some other of the hotels listed at the end of this article.

(3) *General Headquarters*, at which the registration of members, commercial exhibits and all General Sessions will be held, will be the Alcazar, situated at the corner of Cathedral and Madison Streets. Baltimore, unfortunately, is not yet the proud possessor of a convention hall or auditorium at all adequate to its needs, nor comparable to the buildings of this sort found in cities of smaller population. Nonetheless, it is felt that the Alcazar will meet all of the requirements of the College meetings; and all of the meetings, exhibits, registration offices, etc., are located on the same floor, and in easy access to one another.

The skeleton outline of the entire Clinical Week is given in the diagram below, and certain points require particular emphasis:

(1) Those who are planning to attend the Clinical Session should arrange to reach Baltimore either Sunday evening, March 22, or Monday morning, March 23, since the morning of March 23 is left entirely open, thereby giving members and guests ample opportunity to get settled in their hotel quarters, register at the official registration office, and secure therefrom their cards for the various clinics and lectures, for which they have previously signed up, as has been the custom in the past. Not only are these details important, but it is equally to be stressed that a full attendance at the first

FIFTEENTH ANNUAL CLINICAL SESSION  
BALTIMORE, MARYLAND, 1931

Time	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
A. M.	March 23	March 24	March 25	March 26	March 27	March 28
9:00 to 12:30	Morning free. Registra- tion. Exhibits, etc.	3rd General Session	5th General Session	6th General Session General Business Meeting	7th General Session	Entire Day in Washington, D. C. Clinics, Inspection Tours, etc. Under Auspices of Medical Departments of Army, Navy, U. S. Public Health Service, and Georgetown University  Full details not yet ready.
12:30 to 2:00 P. M.	Lunch	.....	.....	.....	.....	
2:00 to 5:00 P. M.	1st General Session	1st Clinical Session	2nd Clinical Session	3rd Clinical Session	4th Clinical Session	
5:00 to 8:00	Dinner	.....	.....		.....	
8:15 to 10:30	2nd General Session	4th General Session	Convoca- tion and Reception to New Members	Annual Banquet	FREE	

General Session, to be held Monday afternoon, is not only desirable but is a courteous acknowledgment to the hosts of the entire meeting. It is the sincere hope of the Program Committee that the hall will be filled when the meeting is called to order sharply at 2 o'clock on the date above mentioned.

(2) It is to be noted that the Convocation this year will be held earlier than has been the custom in the past. Further reference to this will be made in a subsequent paragraph.

(3) It is to be noted that the Clinical Sessions of the meeting will occur in the afternoon, rather than in the morning. This plan has been adopted particularly for the reason that it interferes much less with the teaching of medical students at the Johns Hopkins Medical School and University of Maryland. It will be remembered that this same plan was followed at the meeting in New Orleans, with apparently just as great

success as when the sessions were reversed.

(4) The Annual Banquet will be held on Thursday evening, March 26, presumably at the Lord Baltimore Hotel; and to this, as in times past, ladies are cordially invited.

(5) After the Clinical Sessions have been finished on Friday, March 27, there will be held a Post-Clinical Session Day in Washington, D. C., for all those who care to attend what promises to be an extremely interesting and valuable meeting there.

#### GENERAL SESSIONS

At the last meeting of the Board of Regents that was held during the Minneapolis Session, it was decided that the President of the College would be held responsible for the programs of the General Sessions, of which there are seven in all. Following the Minneapolis meeting, the Executive Secretary of the College, Mr. Loveland, sent out a questionnaire to all of the Fellows and

Associates of the College, asking for ideas and suggestions for the improvement or alteration of subsequent programs. Many replies of value were received, and the answers analyzed; and an attempt has been made by your President to embody as many of the suggestions submitted as possible in the construction of the General Sessions Program. The main changes that he has attempted to make may be briefly summarized, as follows:

(1) The number of papers in the General Sessions will be fewer than has hitherto been the case—probably never in excess of eight papers, of a maximum of twenty minutes each, in any of the morning sessions, which will run from 9 until 12:30.

(2) The morning sessions will be broken mid-way by an intermission of thirty minutes, which will provide not merely a period of relaxation for the audience but will afford an opportunity for every member of the College to make a careful inspection of all of the exhibits. The importance of this cannot be over-emphasized, for it should be pointed out that the exhibits go a long way toward defraying the expenses of the Annual Clinical Session itself; and, moreover, the exhibits offered are invariably worthwhile, from the standpoint of the internist. It has been none too easy a task to assemble as many exhibits as Mr. Loveland has been successful in securing, partly for the reason that exhibitors are aware of the fact that the members of the College will probably be away from the exhibition hall at least half of each day of the Session. It is, therefore, only fair to urge that interest in the exhibits be intensely manifested at all possible times, but particularly during these intermissions which have been provided for just this purpose.

It will perhaps be of interest to know the general method that has been employed in attempting to provide interesting General Sessions. In the first place, the programs of the preceding three meetings were all carefully analyzed, in terms of subjects covered and of individual presenting essays. This analysis revealed several important and interesting facts: particularly, that in the last two years certain subjects had been, if anything, over-handled—as, for instance, ar-

ticles on tuberculosis and hypertension; and, second, the fact that the same individual had presented papers on two and sometimes on three succeeding programs. It was thought wise, therefore, to endeavor to provide a series of articles which dealt as much as possible with new subjects; and, furthermore, it was decided that an individual who had appeared twice within the last preceding three years would not be invited to present a paper at this particular Session. This plan seemed manifestly fair to all to whom the problem was presented.

In the attempt to secure the greatest possible number of submitted titles, the following general method has been employed:

(1) Personal letters have been sent to a great many individuals, whether members of the College or not, throughout the entire United States and Canada.

(2) A letter was sent to the Governor of every state and territory, asking that he in turn submit the names of all Fellows, or of individuals not members of the College, in his State, who, in his opinion, might have material interesting and worthy of presentation before the College; and to every such person a letter was subsequently sent, requesting that the individual in question submit a title or titles of papers which he might care to present. It was clearly pointed out at the time that all of these letters were sent, that the mere submission of a title or titles in no way obligated the Program Committee to accept them.

The result of this extensive correspondence with men all over the country has been the submission of a great many papers, doubtless of both worth and practical interest. At this writing only a few have been finally accepted, and the final selection will be deferred as late as possible, in order that the Program Committee will have the greatest possible amount of material to select from, in its endeavor to secure new subjects, new authors and wide geographical representation. The total number of papers that can be accepted will be between forty-five and fifty, at the most; and it must be apparent that the responsibility for the final selection is no easy one, nor will final selection be the result of personal ideas and opinions, by any means. The hope is expressed that

those who have shown their willingness to read papers will clearly understand, and entertain no hard feelings, if it is found wise to reject their proposed addresses.

The number of possible symposia of great interest is very large. Under consideration at the present time are symposia on blood diseases, oxygen therapy, diseases of the liver, recent advances in endocrinology with particular reference to the newer work on supra-renal extracts, myocarditis, and several others which it is not necessary to mention. The greatest difficulty is to know which of the many equally valuable and interesting ones to accept; obviously, the individual tastes of everyone cannot be met.

#### CLINICAL SESSIONS

To Doctor Maurice C. Pincoffs, Professor of Medicine at the University of Maryland, was delegated the task of arranging for all of the Clinical Sessions. Baltimore has but two medical institutions of learning; namely, Johns Hopkins and the University of Maryland itself. Scattered throughout the city are many modern and excellently run hospitals, in which, however, little if any active teaching is done, at least in conjunction with either of the two Medical Schools. Obviously, the focus of greatest attraction will be the various departments at the Johns Hopkins Hospital and Medical School; and it should be stated at this time that the Heads of all of the Departments of this institution have expressed and are showing an enthusiastic interest in the construction of a program which will open all of the facilities of this enormous plant to the visiting members of the College. The active organization and work, in so far as it concerns the Johns Hopkins Hospital, is under the able administration of Doctor Alan M. Chesney, Dean of the Medical School, and a committee appointed by him. A similar committee, acting under Doctor Pincoffs, will supervise the Clinical Programs to be held at the University of Maryland and its affiliated Hospital. In addition, clinics, ward walks, laboratory demonstrations and the like will be held in many of the non-teaching hospitals of the city, such as the Union Memorial Hospital, Saint Agnes Hospital, at which Doctor Joseph C. Bloodgood does

so much of his work, the Municipal Hospitals, and several of the more private institutions, such as the Howard A. Kelly Hospital, noted particularly for its radium activities, and the Sheppard and Enoch Pratt Hospital, which is one of the most modern dealing with psychiatric problems. This does not by any means exhaust the list.

It has been customary in former meetings to have a certain number of clinics given by distinguished out-of-town clinicians, either Fellows of the College or invited guests; and this custom will be followed again this year, in all likelihood.

It should be further noted that the program, in so far as it concerns Johns Hopkins, will include both the pre-clinical as well as the clinical facilities: the work of the Harriet Lane Home in Pediatrics; the Wilmer Institute for Diseases of the Eye; the Phipps Psychiatric Institute, headed by Doctor Adolf Meyer; and, moreover, the surgical facilities of the Hospital are already being marshalled for the presentation of such border-line problems as are of equal interest to surgeons and internists alike. The Johns Hopkins School of Hygiene and Public Health, with Doctor William H. Howell as its Director, will provide its own program of subjects and demonstrations of interest particularly to Public Health workers and those deeply interested in all lines of Preventive Medicine. Last, but by no means least, the new William H. Welch Department of Medical History will offer a program unique in the annals of the College. As above stated, final details as to topics, clinicians giving them, etc., have not yet been worked out in any of the hospitals; but from the above it can readily enough be seen that plenty can and will be provided to suit the tastes and interests of everyone.

#### CONVOCATION

The Annual Convocation of the College, for the induction of new members, as Masters or Fellows, will be held on Wednesday evening, March 25, at a time and place subsequently to be announced. It is felt that this is, or at least should be, the most formal gathering which the College holds during its Clinical Session; and it is, therefore, earnestly urged that all members and those



to be inducted will appear in evening dress on this occasion, at which time the annual Presidential Address is to be given. Following the Convocation, it is hoped that an appropriate reception to the new members can be held, affording them a chance to meet and know not only the Officers of the College, but also to mingle with those who have been members for varying periods of time. Just how this can best be worked out is still under consideration, but, again, it is hoped that this meeting will be fully attended.

#### ANNUAL BANQUET

As previously stated, this will be held, in all likelihood, at the Lord Baltimore Hotel on the evening of March 26, and at it all members, their wives and guests are urged to be present. The function of such a banquet, it would seem, should be not only a pleasant evening of social intercourse, but it should also provide a message of educational importance to all assembled; and with this in mind, it is now thought that the banquet will be addressed by probably a single speaker of some national or international fame and importance, rather than having the customary after-dinner speeches made by a number of individuals.

#### BUSINESS MEETING

The last half or three-quarters of an hour on the morning of March 26 will be set aside for the holding of the Annual Business Meeting of the College, at which all Fellows and Masters are earnestly urged to be present, so that they may hear in person reports as to the administration and financial status of the College. At this meeting the Nominating Committee, appointed by the President one month after the last General Session, will hand in its nominations for officers, Regents and Governors for the ensuing year; and, finally, on this occasion the incoming President, Doctor S. Marx White, of Minneapolis, will be inducted into office. It is fitting and proper that his induction be marked by a full attendance.

#### LADIES ENTERTAINMENT COMMITTEE

It is hoped and presumed that the Baltimore Session will be graced by the presence of many of the wives of the attending members of the College. Baltimore has long

been famed for its hospitality, and it is an assured fact that an interested and hospitable Ladies Entertainment Committee will see to it that all visiting ladies are interestingly occupied during their stay in Baltimore. Like many other committees, the final plans have not yet been drafted; but no doubt need be entertained as to their fitness and pleasure.

#### POST-SESSION WASHINGTON DAY

It was felt that a great many of the members, particularly those coming from some distance, would not wish to return without paying a visit to the National Capital, particularly if some of the unusual medical facilities of that city could be assembled for their interest and instruction. With this in mind, the matter was taken up with Doctor William Gerry Morgan, President of the American Medical Association and Governor of the American College of Physicians for the District; and through his influence a luncheon was recently held in Washington, at which a number of men of national importance were present, including Surgeon General Ireland, of the Army; Doctor Hugh S. Cummings, Surgeon General of the United States Public Health Service; Doctor C. M. Griffith, Medical Director of the United States Veterans Bureau; Doctor W. A. White, Superintendent of Saint Elizabeth's Hospital; a representative from the United States Naval Medical School, and others, including the President of the Medical Society of the District of Columbia. These men enthusiastically offered their heartiest coöperation in the preparation of a memorable Washington Day, and the number of interesting possibilities was so great that it seemed wise, almost, to change the entire meeting from Baltimore to Washington itself. The facilities of Saint Elizabeth's Hospital and its unusual opportunities of psychiatric study, the Library of the Surgeon General, Army Medical Center, Army Medical School, Walter Reed Hospital, the Smithsonian Museum, the Institute of Public Health, will all be available in a plan which yet remains to be worked out; and this, in turn, will depend largely upon the number of members who express their desire and intention to attend the Washington Meeting.



Such, in schematic form, is the general lay-out for the forthcoming meeting. It is hoped that the lack of specific details will at this time incite rather than dampen further interest in the meeting itself. At least

it can be truthfully stated that Baltimore's welcome will be a wholehearted and unstinting one, and it is believed that all who come will leave repaid.

#### LIST OF BALTIMORE HOTELS

The LORD BALTIMORE HOTEL will be the headquarters hotel for Officers, Regents and Governors, and so far as facilities permit, will accommodate other members and guests of the College. Reservations that the LORD BALTIMORE HOTEL cannot fill, will be referred immediately to some other hotel conveniently located. Those who plan to attend the Baltimore Clinical Session should apply directly for reservations to the hotel of their choice.

(All Prices are for Rates per Day, European Plan)

#### LORD BALTIMORE, Baltimore and Hanover (Headquarters)

Single room with bath.....	\$3.50 to \$ 6.50
Double room with bath.....	5.50 to 10.00

#### ALTAMONT, Eutaw Place and Lanvale St.

Single room without bath.....	2.50
Single room with bath.....	3.00 to 3.50
Double room without bath.....	4.00
Double room with bath.....	5.00 to 6.00

#### ARUNDEL, Charles St. and Mt. Royal

Single room without bath.....	2.00 to 2.50
Single room with bath.....	2.50 to 3.50
Double room without bath.....	3.00 to 3.50
Double room with bath.....	5.00 to 6.00

#### BELVEDERE, Charles and Chase Sts.

Single room with bath.....	5.00 to 6.00
Double room with bath.....	7.00 to 12.00

#### EMERSON, Baltimore and Calvert Sts.

Single room without bath.....	2.50
Single room with bath.....	3.00 to ....
Double room without bath.....	4.00
Double room with bath.....	4.50 to ....

#### KERNAN, Franklin and Howard Sts.

Single room without bath.....	2.00 to 3.00
Single room with bath.....	2.50 to 3.50
Double room without bath.....	3.00 to 4.00
Double room with bath.....	4.00 to 6.00

#### MT. ROYAL, Mt. Royal Ave. and Calvert

Single room without bath.....	2.00 to 2.50
Single room with bath.....	3.00 to 3.50
Double room without bath.....	4.00 to 4.50
Double room with bath.....	5.00 to 6.00

#### NEW HOWARD, Howard St. and Baltimore

Single room without bath.....	2.50 to 3.00
Single room with bath.....	3.00 to 3.50
Double room without bath.....	4.00 to 5.00
Double room with bath.....	5.00 to 6.00

**RENNERT, Saratoga and Liberty Sts.**

Single room without bath.....	2.50 to	3.00
Single room with bath.....	3.00 to	5.00
Double room without bath.....	4.00 to	6.00
Double room with bath.....	5.00 to	8.00

**SOUTHERN, Light and Redwood**

Single room with bath.....	3.00 to	6.00
Double room with bath.....	5.00 to	8.00

**STAFFORD, Charles and Madison Sts.**

Single room without bath.....	2.50 to	3.00
Single room with bath.....	4.00 to	5.00
Double room without bath.....	4.00 to	5.00
Double room with bath.....	6.00 to	8.00

**BOARD OF REGENTS MEETING**

LOUISVILLE, Ky.

NOVEMBER 11, 1930

The Board of Regents of the American College of Physicians met at Louisville, Ky., November 11, on the occasion of the twenty-fourth annual meeting of the Southern Medical Association. President Sydney R. Miller, Doctors F. M. Pottenger, John A. Lichty, S. Marx White, Clement R. Jones, George Morris Piersol, James H. Means, James S. McLester, David P. Barr, Maurice C. Pincoffs, Walter L. Bierring, George E. Brown, John H. Musser, W. Blair Stewart and Mr. E. R. Loveland, Executive Secretary, were present.

The Committee on Credentials for Fellowship, consisting of President Miller, Dr. George Morris Piersol, Chairman, Dr. John A. Lichty, Dr. S. Marx White and Dr. James S. McLester, met on the previous day, November 10, to complete the investigation of 178 candidates. Of this number, the following list was elected by the Board of Regents. In this list is indicated the proposer's name under one, the seconder's name under two, and the endorser's name under three:

**ARIZONA***Phoenix*

Fred G. Holmes

1. Allen K. Krause
2. James Alex. Miller
3. W. Warner Watkins

Earle Wood Phillips

1. Samuel Watson
2. Francis M. Pottenger
3. W. Warner Watkins

*Tucson*

Stirley Casper Davis

1. Samuel Watson
2. Russell J. Callander
3. W. Warner Watkins

**ARKANSAS***Hot Springs National Park*

Harley J. Hallett (M.C., U.S.A.)

1. R. D. Harden
2. George R. Callender
3. M. W. Ireland

**CALIFORNIA***Colfax*

Charles Joseph Durand

1. Robert A. Peers
2. Charles C. Browning
3. Egerton Crispin

*Los Angeles*

Harry Welrose Coffin

1. Charles C. Browning
2. Carl R. Howson
3. Egerton Crispin

Madison J. Keeney

1. Thomas J. Orbison
2. John V. Barrow
3. E. J. G. Beardsley

John Mark Lacey

1. Charles C. Browning
2. Carl R. Howson
3. Egerton Crispin

*Palo Alto*

Percival G. Lasché (U.S.V.B.)

1. Hugo Mella
2. Winthrop Adams
3. Philip B. Matz

*Riverside*

- Paul Edward Simonds  
 1. Charles C. Browning  
 2. Carl R. Howson  
 3. Egerton Crispin

*San Diego*

- William Hulbert Barrow  
 1. Robert Pollock  
 2. Wm. Fitch Cheney  
 3. Egerton Crispin  
 Addison Eugene Elliott  
 1. Lyell C. Kinney  
 2. James F. Churchill  
 3. Egerton Crispin

*San Francisco*

- William Charles Munly (M.C., U.S.A.)  
 1. P. M. Ashburn  
 2. R. D. Harden  
 3. M. W. Ireland  
 Philip Hale Pierson  
 1. Francis M. Pottenger  
 2. Wm. J. Kerr  
 3. Hans Lisser

*San Pedro*

- Forrest Martin Harrison (M.C., U.S.N.)  
 1. P. F. Dickens  
 2. E. E. Smith  
 3. C. E. Riggs

*Woodland*

- Delos Schuyler Pulford  
 1. F. F. Gundrum  
 2. Robert A. Peers  
 3. Egerton Crispin

## COLORADO

*Denver*

- John Thomas Aydelotte (M.C., U.S.A.)  
 1. C. J. Gentzkow  
 2. H. C. Coburn, Jr.  
 3. M. W. Ireland

## CONNECTICUT

*Bristol*

- Ralph Augustus Richardson  
 1. C. Brewster Brainard  
 2. Orin R. Witter  
 3. Henry F. Stoll

*Hartford*

- Augustus Roi Felty  
 1. George Blumer  
 2. Orin R. Witter  
 3. Henry F. Stoll

## James Elder Hutchison

1. Orin R. Witter  
 2. C. Brewster Brainard  
 3. Henry F. Stoll

## Isaac William Kingsbury

1. George Blumer  
 2. Orin R. Witter  
 3. Henry F. Stoll  
 G. Gardiner Russell  
 1. Orin R. Witter  
 2. C. Brewster Brainard  
 3. Henry F. Stoll

*Meriden*

- Cole B. Gibson  
 1. Thomas P. Murdock  
 2. C. Brewster Brainard  
 3. Henry F. Stoll

*New Haven*

- Francis Gilman Blake  
 1. George Blumer  
 2. Orin R. Witter  
 3. Henry F. Stoll

*Norwich*

- Hugh Baird Campbell  
 1. Orin R. Witter  
 2. C. Brewster Brainard  
 3. Henry F. Stoll

*Shelton*

- Edward James Lynch  
 1. Thomas P. Murdock  
 2. Daniel P. Griffin  
 3. Henry F. Stoll

## DELAWARE

*Wilmington*

- Bartholomew M. Allen  
 1. E. J. G. Beardsley  
 2. Olin S. Allen  
 3. George Morris Piersol  
 William Henry Kraemer  
 1. Henry K. Mohler  
 2. Elmer H. Funk  
 3. E. J. G. Beardsley

## DISTRICT OF COLUMBIA

*Washington*

- James Earle Ash (M.C., U.S.A.)  
 1. George R. Callender  
 2. R. D. Harden  
 3. M. W. Ireland

George Franklin Aycock (M.C., U.S.A.)

1. Ernest R. Gentry
2. George R. Callender
3. M. W. Ireland

Arden Freer (M.C., U.S.A.)

1. Ernest R. Gentry
2. George R. Callender
3. M. W. Ireland

Joseph Burton Glenn

1. William Earl Clark
2. William Cabell Moore
3. Wm. Gerry Morgan

Charles Clark Hillman (M.C., U.S.A.)

1. Ernest R. Gentry
2. George R. Callender
3. M. W. Ireland

James Alexander Lyon

1. Edgar P. Copeland
2. Thomas S. Lee
3. Wm. Gerry Morgan

Paul Edgar McNabb (M.C., U.S.A.)

1. Charles F. Craig
2. P. M. Ashburn
3. M. W. Ireland

John William Meehan (M.C., U.S.A.)

1. Charles F. Craig
2. P. M. Ashburn
3. M. W. Ireland

Charles R. Mueller (M.C., U.S.A.)

1. Ernest R. Gentry
2. George R. Callender
3. M. W. Ireland

Edward Thomas B. Weidner (M.C., U.S.A.)

1. W. Lee Hart
2. George R. Callender
3. M. W. Ireland

#### FLORIDA

*Jacksonville*

Louie Limbaugh

1. R. H. McGinnis
2. Julius Friedenwald
3. Maurice C. Pincoffs

*Miami Beach*

Charles Frederic Roche

1. G. H. Benton
2. Paul D. White
3. T. Z. Cason

*Orlando*

Spencer Augustus Folsom

1. Allen H. Bunce
2. E. C. Thrash
3. James D. Love

Meredith Mallory

1. W. C. Blake
2. John H. Peck
3. Walter L. Bierring

#### GEORGIA

*Atlanta*

Augustus Benjamin Jones (M.C., U.S.A.)

1. P. M. Ashburn
2. R. D. Harden
3. M. W. Ireland

*Thomasville*

Ernest F. Wahl

1. W. S. Thayer
2. Sydney R. Miller
3. Russell H. Oppenheimer

#### ILLINOIS

*Oak Park*

William E. Kendall

1. Louis L. Syman
2. Edward W. Hollingsworth
3. James G. Carr

*Peoria*

Orville Barbour

1. George W. Parker
2. Fred M. Meixner
3. Samuel E. Munson

#### INDIANA

*Gary*

Earl Donovan Skeen

1. H. M. English
2. C. M. Reyher
3. Roscoe H. Beeson

*Indianapolis*

Edgar F. Kiser

1. Herman M. Baker
2. Bayard G. Keeney
3. Roscoe H. Beeson

#### IOWA

*Des Moines*

Addison Carey Page

1. John H. Peck
2. Tom B. Throckmorton
3. Walter L. Bierring

*Ottumwa*

Frederick Alexander Hecker

1. Edward Tyler Edgerly
2. John H. Peck
3. Walter L. Bierring

## KENTUCKY

*Louisville*

Harry Stucky Frazier

1. C. W. Dowden
2. J. Rowan Morrison
3. E. B. Bradley

James Murray Kinsman

1. C. W. Dowden
2. Charles G. Lucas
3. E. B. Bradley

Hulbert Viars Noland

1. C. W. Dowden
2. Charles G. Lucas
3. E. B. Bradley

Thomas Cook Smith

1. C. W. Dowden
2. Charles G. Lucas
3. E. B. Bradley

## LOUISIANA

*Morgan City*

Charles Camille deGravelles

1. Daniel N. Silverman
2. Charles J. Bloom
3. J. H. Musser

## MAINE

*Portland*

Charles Bradford Sylvester

1. Eugene H. Drake
2. Mortimer Warren
3. E. W. Gehring

## MARYLAND

*Baltimore*

Walter A. Baetjer

1. Lewellys F. Barker
2. Sydney R. Miller
3. Harvey G. Beck

John Lanahan Dorsey

1. Lewellys F. Barker
2. Sydney R. Miller
3. Harvey G. Beck

Thomas Barnes Futchter

1. Harvey G. Beck
2. Maurice C. Pincoffs
3. Sydney R. Miller

Louis Hamman

1. Harvey G. Beck
2. Maurice C. Pincoffs
3. Sydney R. Miller

John T. King, Jr.

1. W. S. Thayer
2. Sydney R. Miller
3. Harvey G. Beck

Lay Martin

1. Thomas R. Brown
2. Sydney R. Miller
3. Harvey G. Beck

A. Ferdinand Ries

1. Julius Friedenwald
2. Andrew C. Gillis
3. Harvey G. Beck

Thomas P. Sprunt

1. Lewellys F. Barker
2. Sydney R. Miller
3. Harvey G. Beck

Henry M. Thomas, Jr.

1. Lewellys F. Barker
2. Sydney R. Miller
3. Harvey G. Beck

## State Sanatorium

Victor F. Cullen

1. Lewellys F. Barker
2. Sydney R. Miller
3. Harvey G. Beck

## MASSACHUSETTS

*Boston*

Helmuth Ulrich

1. William D. Reid
2. Conrad Wesselhoeft
3. J. H. Means

William H. Watters

1. William D. Reid
2. Edward S. Calderwood
3. J. H. Means

*Waltham*

Dwight O'Hara

1. William B. Breed
2. Maurice Fremont-Smith
3. Roger I. Lee

## MICHIGAN

*Ann Arbor*

Louis Harry Newburgh

1. Alpheus F. Jennings
2. Douglas Donald
3. Charles G. Jennings

*Detroit*

- John Everett Gordon  
 1. Alpheus F. Jennings  
 2. Douglas Donald  
 3. Charles G. Jennings

*Flint*

- Myrton Shaw Chambers  
 1. W. H. Marshall  
 2. M. S. Knapp  
 3. Charles G. Jennings

*Grand Rapids*

- Harold Clinton Robinson  
 1. Thomas D. Gordon  
 2. Joseph B. Whinery  
 3. Aldred Scott Warthin

## MINNESOTA

*Rochester*

- Edgar Vannice Allen  
 1. Philip S. Hench  
 2. S. Franklin Adams  
 3. George E. Brown

and

E. L. Tuohy

David Garrison Christ

1. A. R. Barnes  
 2. L. G. Rowntree  
 3. E. L. Tuohy

Charles Koran Maytum

1. Fred W. Gaarde  
 2. P. P. Vinson  
 3. George E. Brown

*St. Paul*

- Edward Schons  
 1. J. A. Lepak  
 2. Charles N. Hensel  
 3. E. L. Tuohy

## MISSOURI

*Kansas City*

- Arthur Charles Clasen  
 1. Wilson A. Myers  
 2. Lindsay S. Milne  
 3. A. Comingo Griffith

Harry Lander Jones

1. P. T. Bohan  
 2. Frank I. Ridge  
 3. A. Comingo Griffith

## NEW JERSEY

*Newark*

- L. Charles Rosenberg  
 1. A. E. Parsonnet  
 2. Asher Yaguda  
 3. Harlow Brooks  
 and  
 W. Blair Stewart

*Pleasantville*

- Clyde Mulhollon Fish  
 1. E. J. G. Beardsley  
 2. Arthur C. Morgan  
 3. W. Blair Stewart

*Trenton*

- Barney Doibe Lavine  
 1. J. J. McGuire  
 2. Wm. S. Collier  
 3. W. Blair Stewart  
 Nathan Swern  
 1. James J. McGuire  
 2. William S. Collier  
 3. W. Blair Stewart

## NEW MEXICO

*Albuquerque*

- John Robert Van Atta  
 1. P. T. Bohan  
 2. Logan Clendening  
 3. L. S. Peters

## NEW YORK

*Brooklyn*

- Louis Harris  
 1. Maurice J. Dattelbaum  
 2. Raymond Clark  
 3. Harlow Brooks

*Jackson Heights*

- Margaret Ruth Reynolds  
 1. Luvia M. Willard  
 2. Marshall Carleton Pease  
 3. James Alex. Miller

*Long Island City*

- Carl Boettiger  
 1. George Forbes  
 2. Christian Wm. Janson  
 3. Harlow Brooks

*New York*

- Louis Faugeres Bishop, Jr.  
 1. Louis F. Bishop  
 2. William Van Valzah Hayes  
 3. Harlow Brooks



Otto H. Leber

1. Walter A. Bastedo
2. Orrin Sage Wightman
3. James Alex. Miller

Henry A. Rafsky

1. Max Einhorn
2. George G. Ornstein
3. Harlow Brooks

Griffith Edwards Thomas (M.C., U.S.N.)

1. W. W. Behlow
2. L. L. Pratt
3. C. E. Riggs

#### *Willard*

Harry Beckett Lang

1. C. Harvey Jewett
2. Harold A. Patterson
3. John A. Lichty

#### NORTH CAROLINA

##### *Chapel Hill*

Isaac Hall Manning

1. L. B. McBrayer
2. W. Bernard Kinlaw
3. C. H. Cocke

##### *Goldshoro*

William Hopton Smith

1. L. B. McBrayer
2. P. P. McCain
3. C. H. Cocke

##### *Raleigh*

William Banks Dewar

1. Paul F. Whitaker
2. Wm. deB. MacNider
3. C. H. Cocke

##### *Sanatorium*

Samuel Moffett Bittinger

1. P. P. McCain
2. L. B. McBrayer
3. C. H. Cocke

##### *Winston-Salem*

John Kerr Pepper

1. Thurman D. Kitchin
2. L. B. McBrayer
3. C. H. Cocke

#### OHIO

##### *Cleveland*

Richard S. Dexter

1. Harry V. Paryzek
2. Charles W. Stone
3. John Dudley Dunham

Charles Thomas Way

1. V. C. Rowland
2. Harry V. Paryzek
3. John Dudley Dunham

#### OKLAHOMA

##### *Oklahoma City*

Hull Wesley Butler

1. L. J. Moorman
2. Arthur W. White
3. Lea A. Riely

##### *Tulsa*

William J. Bryan, Jr.

1. L. J. Moorman
2. Clarence Manning Grigsby
3. Lea A. Riely

#### PENNSYLVANIA

##### *Beaver*

Fred Bailey Wilson

1. R. R. Snowden
2. George W. Grier
3. E. Bosworth McCready

##### *Bellevue*

Thomas Alfred Miller

1. R. R. Snowden
2. Frederick B. Utley
3. E. Bosworth McCready

##### *Bethlehem*

Harvey Oscar Rohrbach

1. Francis J. Dever
2. Edgar M. Green
3. E. J. G. Beardsley

##### *Lancaster*

Roland Nicholas Klemmer

1. Truman G. Schnabel
2. George Morris Piersol
3. E. J. G. Beardsley

##### *Lansdowne*

Eugene Allen Case

1. E. J. G. Beardsley
2. Arthur C. Morgan
3. George Morris Piersol

##### *Philadelphia*

Mitchell Bernstein

1. Arthur C. Morgan
2. Isadore Kaufman
3. E. J. G. Beardsley

Ward Brinton

1. E. J. G. Beardsley
2. Truman G. Schnabel
3. George Morris Piersol

**Jacob Morris Cahan**

1. Alfred Gordon
2. Isadore Kaufman
3. E. J. G. Beardsley

**Louis H. Clerf**

1. E. J. G. Beardsley
2. Elmer H. Funk
3. George Morris Piersol

**David Alexander Cooper**

1. David Riesman
2. Truman G. Schnabel
3. E. J. G. Beardsley

**John Thompson Farrell, Jr.**

1. H. K. Mohler
2. Elmer H. Funk
3. E. J. G. Beardsley

**Thomas Fitz-Hugh, Jr.**

1. David Riesman
2. Truman G. Schnabel
3. E. J. G. Beardsley

**Arthur Haddon Hopkins**

1. E. J. G. Beardsley
2. Truman G. Schnabel
3. George Morris Piersol

**Horace H. Jenks**

1. E. J. G. Beardsley
2. H. Brooker Mills
3. George Morris Piersol

**Willis F. Manges**

1. E. J. G. Beardsley
2. Elmer H. Funk
3. George Morris Piersol

**Samuel Watkins Sappington**

1. Carl V. Vischer
2. E. Roland Snader, Jr.
3. George Morris Piersol

**Edward A. Strecker**

1. E. J. G. Beardsley
2. Charles W. Burr
3. George Morris Piersol

**William Daniel Stroud**

1. E. J. G. Beardsley
2. Alfred Stengel
3. George Morris Piersol

**Josephus Tucker Ullom**

1. David Riesman
2. Truman G. Schnabel
3. E. J. G. Beardsley

**Charles Christian Wolferth**

1. E. J. G. Beardsley
2. Alfred Stengel
3. George Morris Piersol

**Pittsburgh****Ellis Mills Frost**

1. J. M. Thorne
2. C. W. Morton
3. E. Bosworth McCready

**George Rufus Lacy**

1. Joseph H. Barach
2. J. M. Thorne
3. E. Bosworth McCready

**Howard Gustav Schleiter**

1. George W. Grier
2. J. M. Thorne
3. E. Bosworth McCready

**Thomas McCance Mabon**

1. Joseph H. Barach
2. J. M. Thorne
3. E. Bosworth McCready

**Charles Howard Marcy**

1. Joseph H. Barach
2. J. M. Thorne
3. E. Bosworth McCready

**Cornelius Collins Wholey**

1. Joseph H. Barach
2. J. M. Thorne
3. E. Bosworth McCready

**Wayne****Henry Field Smyth**

1. E. J. G. Beardsley
2. Charles W. Burr
3. George Morris Piersol

**West Chester****Henry Pleasants, Jr.**

1. E. J. G. Beardsley
2. Truman G. Schnabel
3. George Morris Piersol

**TENNESSEE****Knoxville****Robert Benton Wood**

1. O. N. Bryan
2. E. R. Zemp
3. J. O. Manier

**Memphis****Arthur F. Cooper**

1. J. B. McElroy
2. Otis S. Warr
3. J. O. Manier

**Edward Gilmer Thompson**

1. Whitman Rowland
2. J. B. McElroy
3. J. O. Manier

## TEXAS

*Dallas*

Henry Morgan Winans

1. D. W. Carter, Jr.
2. Homer Donald
3. C. M. Grigsby

*El Paso*

Michael Andrew Daily (M.C., U. S.A.)

1. R. D. Harden
2. George R. Callender
3. M. W. Ireland

James Warren Laws

1. Charles M. Hendricks
2. Will S. Horn
3. C. M. Grigsby

## VERMONT

*Burlington*

Paul Kendrick French

1. Harry R. Ryan
3. C. H. Beecher

## VIRGINIA

*Petersburg*

Mason Romaine

1. Milton A. Bridges
2. Dean B. Cole
3. J. Morrison Hutcheson

*Quantico*

Ernest William Brown (M.C., U.S.N.)

1. Otis Wildman

2. J. M. McCants

3. C. E. Riggs

*Richmond*

Charles Martin Caravati

1. Paul F. Whitaker
  2. Dean B. Cole
  3. J. Morrison Hutcheson
- James Hunt Royster
1. Dean B. Cole
  2. Beverley R. Tucker
  3. J. Morrison Hutcheson

*Staunton*

Alexander F. Robertson, Jr.

1. E. J. G. Beardsley
2. Dean B. Cole
3. J. Morrison Hutcheson

## BRITISH WEST INDIES

## Jamaica

*Kingston*

Arthur William Grace

1. George A. Pemberton Wright
2. C. D. Briscoe
3. Wm. M. James

## CANAL ZONE

*Balboa Heights*

Charles Kettig Berle (M.C., U.S.A.)

1. P. M. Ashburn
2. R. D. Harden
3. M. W. Ireland

The Executive Secretary reported the following deaths:

*Fellows*

Robert H. Babcock	Chicago, Ill.	June 28, 1930
William P. Bowman	Los Angeles, Calif.	October 20, 1930
Murrett F. DeLorme	Brooklyn, N. Y.	September 8, 1930
J. Edward Harbinson	Woodland, Calif.	April, 1930
Preston M. Hickey	Ann Arbor, Mich.	October 30, 1930
Robert T. Hood	Pittsburgh, Pa.	October 5, 1930
William J. Kay	Lapeer, Mich.	April 16, 1930
Guy L. Kiefer	Lansing, Mich.	May 8, 1930
Joseph Patton	Chicago, Ill.	April 16, 1930
Robert Pollock	San Diego, Calif.	June 2, 1930
William C. Rucker	New Orleans, La.	May 22, 1930
Anthony A. Rutz	Brooklyn, N. Y.	May 3, 1928
Cuthbert Thompson	Louisville, Ky.	June 23, 1930
Antonio D. Young	Oklahoma City, Okla.	June 3, 1930

*Associates*

Isidor Betz	Brooklyn, N. Y.	July 13, 1930
Nicholas Lukin	New York, N. Y.	June 10, 1930
Frank C. Hollister	New York, N. Y.	November 30, 1929

The following resignations were accepted:  
*Fellows*

Frederick C. Harrison	Toronto, Ont.
George H. Whipple	Rochester, N. Y.

*Associates*

Aaron C. Conaway	Marshalltown, Ia.
Anthony H. Lange	Detroit, Mich.
James B. Waddell	Wheaton, Ill.

Dr. Hugh A. Beam, of Moline, Ill., was reinstated as a Fellow of the College.

The Executive Secretary was instructed to urge the gift of books of which members of the College are authors to the College Memorial Library, rather than the gift of reprints and miscellaneous articles. It was pointed out that a Memorial Library consisting of books published by Fellows and Associates of the College would be of great interest and worth to the College, whereas reprints are so numerous as to be difficult of suitable housing and indexing, and probably can be very infrequently referred to.

The Executive Secretary reported on a long list of publications contributed to the College Library, the majority of which were reprints. Dr. Beverly R. Tucker (Fellow), Richmond, Va., had contributed his book, "The Gift of Genius," which was the only book received since the previous Regents' meeting.

The Committee on Hospital Efficiency was by resolution discontinued, because of its lack of activity at the present time.

The work and report of a previous Committee on Postgraduate Medical Instruction was reviewed, and the desirability of having the College maintain a complete outline of all the approved sources of postgraduate medical courses offered throughout the United States and Canada each year was discussed. The following resolution, thereafter, was adopted:

"RESOLVED, that the President appoint a Committee of three to investigate the advisability and feasibility of the College studying the facilities of the United States and Canada for postgraduate instruction."

Dr. James H. Means, Boston, in the absence of the Chairman, Dr. Jonathan C. Meakins, presented a preliminary report for the Phillips Memorial Committee. Thirty-

one theses had been submitted before August 31, for competition for the 1931 award. These theses were still in the process of being read and classified as to rank. The Committee was instructed to consider the present rules governing the award, with a view to revising them, in the light of this year's experience, for future years. The Committee was instructed to consider also the matter of making up the announcement for 1932.

The Executive Secretary presented a financial report on *ANNALS OF INTERNAL MEDICINE*. Heretofore the journal has operated at some deficit, but through increased circulation and the adding of advertising, Volume III, which was completed with the June, 1930, Issue, showed a net surplus of \$554.94.

Reports on the arrangements for the Fifteenth Annual Clinical Session at Baltimore were made by Dr. Maurice C. Pincoffs, General Chairman of Arrangements, Dr. Sydney R. Miller, Chairman of the General Sessions, and by Mr. Loveland, Executive Secretary. News notes concerning the program will be found elsewhere in this issue of the journal. However, it may be interesting to know that President Miller made a complete analysis of the previous three programs, showing the scope of topics and the names of each contributor. These analyses showed a considerable amount of repetition, not only in subjects, but in the names of contributors. It was the opinion of the Board of Regents, as well as many Fellows of the College, that the Baltimore program should reduce to a minimum the amount of repetition, both in topics and contributors. President Miller reported he had received more than three hundred suggestions of topics and names for the general program, out of which he and his Committee can select only about fifty papers and separate authors.

In further discussion, it was recommended that the Convocation of the College be held on Wednesday evening of the clinical week, instead of Thursday evening. The convocation, being the occasion of the annual address by the President, should be held before the General Business Meeting on Thursday, at which time the new President is inducted.

It was further recommended that a reception by the President and Regents to the new members be held immediately following the Convocation. All newly elected Fellows shall be notified that they are expected to attend the Convocation and the reception, and to come in evening clothes.

After proper discussion, the following motion was regularly made, seconded and adopted:

"RESOLVED, that the President, Officers and Executive Secretary be authorized to furnish any Fellow visiting important medical gatherings with proper credentials."

Fellows of the College desiring letters of identification as official delegates to various important medical congresses should apply to the Executive Secretary for such letters.

President Miller was advised to take under advisement the matter of scientific exhibits, as well as technical or commercial exhibits, at the Baltimore Clinical Session.

Excluding elections made at this meeting, the College membership on November 11 consisted of 6 Masters, 1795 Fellows and 500 Associates; a total of 2301. In point of membership, New York ranked first, with 291; Pennsylvania second, with 206; California third, with 156; Michigan fourth, with 141; Illinois fifth, with 123; Ohio sixth, with 118; and Minnesota seventh, with 104.

Dr. Edgar Erskine Hume, a Fellow of the College, proposed a method of indicating Fellowship in the College on the sleeve of academic gowns through the use of a Stafford knot. The matter was briefly discussed, and the following resolution regularly adopted:

"RESOLVED, that Dr. Hume's proposal be referred to a Committee of three to report back to the Regents at the next meeting."

Dr. Albert A. Getman (Fellow), Syracuse, N. Y., was reported as a new Life Member, as of June 4, 1930.

To meet the requirements of the By-Laws, which state that "it shall be the duty of the Board of Regents to provide a plan for securing an adequate endowment . . .," the Board of Regents regularly adopted the following resolution:

"RESOLVED, that the Finance Committee be authorized to carry on such activities as in

their judgment will stimulate Life Membership."

Members of the present Finance Committee were reviewed, and it was resolved that a new Finance Committee of five, including the two Regents who are now members of the Committee, be appointed by the President, and that the Committee shall be authorized to formulate for the Board of Regents a method for fixing a term of service for a standing Finance Committee.

In order that the provision of the By-Laws shall be carried out in regard to having a joint meeting of the Committee on Credentials for Fellowship and the Committee on Credentials for Associateship, for the purpose of co-ordinating the standards of admission, and also for the purpose of preparing recommendations for election to Associateship and Fellowship at the Baltimore Clinical Session, it was

"RESOLVED, that the two Committees on Credentials are authorized to hold a joint meeting one month in advance of the Baltimore Clinical Session."

The next meeting of the Board of Regents was set for March 22, 1931, at Baltimore.

Fellows appearing on the program of the Illinois Tuberculosis and Public Health Association were Dr. James Stuart Pritchard of Battle Creek, Michigan, Dr. Cecil Jack of Decatur, and Dr. Fred M. Meixner of Peoria, Illinois.

Dr. Pritchard and Dr. Meixner discussed the "Causes of Cough" and Dr. Jack, "The County Tuberculosis Sanatorium in the City."

In the November Issue of the American Journal of the Medical Sciences, the following Fellows are authors of original articles indicated:

Dr. Cyrus C. Sturgis, Ann Arbor, Mich.: (with Dr. Raphael Isaacs) "Treatment of Pernicious Anemia with Desiccated, Defatted Stomach"

Dr. William A. Groat, Syracuse, N. Y.: "Mitosis in Myeloblasts in Peripheral Blood"

Dr. Roger S. Morris, Cincinnati, Ohio: (with Dr. Stanley E. Dorst) "Bacterial Hypersensitivity of the Intestinal

Tract. Its Treatment with Autogenous Vaccine and Sodium Ricinoleate"

Dr. Julius Friedenwald and Dr. Theodore H. Morrison, both of Baltimore, Md.: "A Clinical Study of Gumma of the Liver"

Dr. Frank N. Allan, Rochester, Minn.: (with Dr. Frances R. VanZant) "Renal Glycosuria, with Ketosis During Surgical Complications"

Dr. Byron D. Bowen, Buffalo, N. Y.: (with Dr. Alvin G. Foord) "Acute Interstitial Pancreatitis in Two Cases of Diabetic Coma"

Dr. I. M. Rabinowitch, Montreal, Que.: (with Dr. A. H. Gordon) "Low Basal Metabolism Following Lobar Pneumonia Associated with Marked Undernutrition"

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Dr. Lucius C. Sanders (Associate), Memphis, addressed the Mississippi County (Ark.) Medical Society, September 9, on cancer of the colon.

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Dr. Robert A. Peers (Fellow), Colfax, Calif., spoke before the San Joaquin County (Calif.) Medical Society, September 4, on "What to Tell the Tuberculous Patient."

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Dr. Emmet F. Horine (Fellow), Louisville, used as his topic, "The Mechanism of the Heart," in an address before the Third District (Ind.) Medical Society at New Albany, October 8.

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Dr. Robert M. Moore (Fellow), Indianapolis, addressed the Elkhart County (Ind.) Medical Society on "Coronary Occlusion," October 2.

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Dr. Jack Witherspoon (Fellow), Nashville, Tenn., addressed the Christian County (Ky.) Medical Society, September 23, on "Duodenal Ulcers."

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Dr. Elliott P. Joslin (Fellow), Clinical Professor of Medicine at Harvard Medical School, was one of the chief speakers at a complimentary dinner given to Francis G. Benedict, Ph.D., Director of the Nutrition Laboratory of the Carnegie Institution of Washington.

Dr. Colonel B. Burr (Fellow), Flint, Mich., was the recipient of the honorary degree of Master of Arts conferred by the University of Michigan Medical School at its eighty-second opening assembly. Dr. Burr was formerly a member of the faculty and the historian of the University. He is the author of "Medical History of Michigan," recently published in two volumes. Dr. Burr is now retired.

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Dr. Ernest E. Irons (Fellow), Dean of Rush Medical College, Chicago, was a participant in the fifth annual clinic of the Highland Park Physicians' Club held December 4.

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Dr. Richard M. McKean (Fellow), Detroit, offered a postgraduate lecture on "Hypertension and Nephritis," October 7, in connection with the first series of graduate courses in medicine and surgery offered under the auspices of the Wayne County (Mich.) Medical Society.

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Dr. S. Marx White (Fellow), Minneapolis, spoke on "Arthritis Deformans" before the Interurban Academy of Medicine at Duluth, recently.

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Dr. John H. Musser (Fellow), New Orleans, addressed the Omaha-Douglas County (Nebr.) Medical Society on "Oral Cavity in Certain Systemic Diseases," October 20.

Dr. Musser also addressed the American Protestant Hospital Association at its meeting in New Orleans, October 17-20.

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At the twenty-fourth annual meeting of the Seventh District Branch Medical Society of the State of New York, held at Penn Yan, September 24, Dr. John L. Eckel (Associate), Buffalo, spoke on "Anterior Poliomyelitis," and Dr. James E. Talley (Fellow), Philadelphia, spoke on "Care of the Heart in Certain Infections."

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Dr. George H. Spivey (Fellow), resigned, as of September 1, as Director of the Winkler County Health Unit to accept another position of similar nature at Phoenix, Arizona.



Dr. Thomas B. Magath (Fellow), Rochester, Minn., is the Editor of the new American Journal of Clinical Pathology, which will be published beginning January, 1931, under the auspices of the American Society of Clinical Pathologists. Among members of the Advisory Editorial Board, are the following Fellows of the American College of Physicians:

Dr. Arthur H. Sanford, Rochester, Minn.  
 Dr. Kenneth M. Lynch, Charleston, S. C.  
 Dr. Walter S. Thomas, Clifton Springs, N. Y.  
 Dr. Charles St. John Butler, Washington, D. C.

The Association of American Medical Colleges held its forty-first annual meeting in Denver, October 14-16. Dr. Charles C. Bass (Fellow), Dean of the Tulane University of Louisiana School of Medicine, was elected Vice President.

Dr. Lawrence R. DeBuys (Fellow), New Orleans, addressed the Childrens' Hospital Association of America at its annual meeting in New Orleans, October 23, on "Management of a Childrens' Service in a General Hospital."

At the Central States Pediatric Society's annual meeting in Memphis, November 7-8, Dr. Maud Loeber (Fellow), New Orleans, spoke on "Evaluation of Gastric Analyses and Stool Examination in a Series of Cases When no other Pathology has been found to Account for Anorexia, Loss of Weight and Capricious Appetite," and Dr. John A. McIntosh (Fellow), Memphis, spoke on "The Relationship of Metazoal and Protozoal Infestation to Vitamin B. Deficiency."

Dr. S. E. Thompson (Fellow), Kerrville, Texas, was elected President of the Southwest Texas District Medical Society at its twenty-fourth semiannual meeting at Corpus Christi, during July, 1930.

Dr. E. Roland Snader, Jr. (Fellow), Philadelphia, after having served as Secretary of the Homeopathic Medical Society of the State of Pennsylvania for five consecutive years, resigned from the office at the

meeting of the Society held at Harrisburg, during September. He was elected to the Board of Trustees.

Dr. G. Hardin Wells (Fellow), Philadelphia, was also elected a member of the Board of Trustees.

Dr. Carl V. Vischer (Fellow), Philadelphia, was elected a Censor for a term of three years.

Dr. David N. Kremer (Fellow), Philadelphia, presented a paper entitled, "Obesity: Observations on Dietary Management" before the Section on Medicine of the College of Physicians.

Dr. Howard L. Hull (Fellow), Elma, Washington, gave an address on "Public Health Problems in which the Citizen should be Interested," October 25, at Menlo, Washington, before the Federation of Women's Clubs. Some 150 women were present at the meeting.

Dr. M. L. Stevens (Fellow), President-Elect of the Medical Society of the State of North Carolina, Asheville; Dr. L. B. McBrayer (Fellow), Secretary-Treasurer of the Medical Society of the State of North Carolina, Southern Pines, and Dr. P. P. McCain (Fellow), Superintendent of the North Carolina State Sanatorium, all delivered addresses at the meeting of the Tenth District Medical Society at Murphy, N. C., October 22.

Dr. McBrayer also addressed the Wayne County Medical Society at Goldsboro, October 3, and the State Nurses Association at Greensboro, October 16.

Acknowledgment is herewith made of the receipt of reprints of publications by the following members:

Dr. J. P. Zohlen (Fellow), Sheboygan, Wis.: 2 reprints—"Cardiospasm and Concomitant Esophageal Diverticulum; Case Report." "Echinococcus Cysts of Abdomen and Lung; Case Report"

Dr. Oliver T. Osborne (Fellow), New Haven, Conn.: 1 reprint—"Medical Education"

Dr. Osborne is the author of the following editorials recently published:

"The Young Physician," appearing in the MEDICAL JOURNAL AND RECORD, September 3, 1930, page 250;

"Intelligence Tests and Psychology," appearing in the MEDICAL JOURNAL AND

RECORD, also September 3, 1930, page 251.

"Medical Education" is another editorial of Dr. Osborne that appeared in the September 17, 1930, issue of the MEDICAL JOURNAL AND RECORD.

### OBITUARY

Dr. Cuthbert Thompson (Fellow), Louisville, Ky.; died, June 23, 1930, of pneumonia; aged, 65 years.

Dr. Thompson was born in Londonderry, Ireland. He attended Magee College, of Londonderry, and Queens College, of Galway. He received his degree of M.B., C.M. from Edinburgh University in 1892. He was Professor of Clinical Medicine at the Hospital College of Medicine and the University of Louisville from 1907 to 1911; Consultant, neurology, Marine Hospital No. 11, U. S. Public Health Service, and a member of the medical staff of St. Joseph's Infirmary.

Dr. Thompson was a member of his county and state medical societies, a Fellow of the American Medical Association, a member of the British Medical Association, and had been a Fellow of the American College of Physicians since 1919. He specialized in Neurology, and was the author of several meritorious published papers in this field.

Dr. Robert Thurlow Hood (Fellow), Pittsburgh, Pa.; died October 5, 1930; aged, 43 years.

In the death of Dr. Hood, the profession and the community has suffered a distinct loss. Dr. Hood was born in Washington County, Pennsyl-

vania, in 1887. After being graduated at Westminster College, he obtained his degree of M.D. from the Medical Department of the University of Pittsburgh in 1914. He began the practice of medicine in Dormont, a suburb of Pittsburgh, and soon after, making a specialty of internal medicine, opened offices in the Westinghouse Building in this city. During the World War, he served in the Army. Last June he became ill with intestinal influenza, this being followed by a psoas abscess which led to his death. Dr. Hood was on the staff of the Western Pennsylvania Hospital, a member of the Allegheny County Medical Society and the Pittsburgh Academy and a fellow of the American Medical Association. He has been a Fellow of the American College of Physicians since 1922. He was a member of the Third United Presbyterian Church, a Mason, and belonged to the Keystone Athletic Club and the Longvue Country Club. Several years ago, Dr. Hood married Miss Eleanor Clark, who survives him with three small sons. He is also survived by his father, the Rev. R. H. Hood, and a brother, Thomas Hood, both of Dormont.

—Furnished by E. Bosworth McCready, M.D., F.A.C.P., Governor for Western Pennsylvania.

# The Biology and Etiology of Cancer\*†

By LEO LOEB, *St. Louis, Mo.*

THE present era in cancer research dates back somewhat more than 30 years. In this paper I must limit myself to a rapid survey of the advances made during this period and to an indication of how I believe the isolated facts thus accumulated can be combined into a consistent theory of cancer.

To state the essential fact, cancer cells are cells which were originally, either ordinary tissue or embryonal cells, and which, under the influence of environmental stimuli, acting in combination with hereditary factors, assume an increased intensity of proliferation; in some cases this proliferation is combined with increased ameboid activity, and it is always associated with certain modifications in metabolism and enzymatic activity and with certain other properties. The characteristic feature of this transformation is the peculiar independence of the cancer cells from all those factors which originally caused the transformation. Even before the end stage has been reached, in which the normal cells have definitely become cancerous, the stimuli are

no longer required for the consummation of the change. Various kinds of stimuli—irritating substances, long-continued mechanical irritations, internal secretions—all have in the end the same effect, provided they act on a responsive substratum. They all stimulate growth and as a result of this continued stimulation they lead ultimately to an excessive activity which is continuous and which we call cancer.

In the strict sense we have not to deal with growth substances which are specific in the origin of cancer. Still certain substances are more effective than others in this respect. As to the nature of the latter, Vaubel suggested definite chemical configurations as characteristic of such substances, and Hammett believes that the sulfhydryl group is particularly effective. In general, we can classify growth promoting substances into two classes: (1) Those which take a normal part in the economy of the organism and to which the organism is more or less adapted, as e.g., hormones and perhaps certain contact substances. It seems that these factors if present in the usual quantity produce cancer only in association with hereditary factors. (2) Pathological stimuli to which the organism is not normally adapted, such as extraneous growth substances, e.g., tar, arsenic, and stimulations of a physical nature,

\*(From the Department of Pathology, Washington University School of Medicine, St. Louis, Mo.).

†Presented in the Symposium on Cancer before the American College of Physicians, Minneapolis, Feb. 13, 1930.

acting as prolonged irritations. To these agencies the organism responds more readily with pathological growth processes, which, step by step, may pass into cancer.

Growth substances of the second type, namely, those to which the body is not adapted, may act not only on adult tissue, but under certain conditions, they can transform also embryonal tissues into cancer, as shown by the experiments of Askanasy, who used for this purpose lipid solvents, and of Murphy and Landsteiner, who added tar in great dilution to embryonic chick tissue and injected the mixture into adult chickens. But successes are only exceptional and they seem to be limited to embryonic tissue implanted into adult organisms. All other farther going claims have not so far been confirmed.

Above we have referred to the importance of the substratum, on which the various stimuli act. As far as we can judge at the present time, the rôle that heredity plays in the etiology of cancer is probably that of making the substratum more responsive to the stimulating agencies. A sensitized tissue, as for instance, the uterine mucosa sensitized by the corpus luteum, responds with increased intensity to various mechanical and chemical stimuli, to which a normal tissue would remain almost indifferent. It will not be necessary for me to discuss in a more detailed way the mode of action of heredity in cancer, inasmuch as this problem will be discussed later by two competent investigators, Dr. Wells and Dr. Warthin. However, inasmuch as my own studies, for many years past, have dealt with this problem, I may

perhaps be permitted to make two further remarks. In the first place, as stated, I believe that, in the production of cancer, heredity interacts, in the large majority of cases, with various stimulating factors in a wide range of combinations. At one end of this range the external factors are acting with such intensity that they alone, or almost alone, can call forth the cancerous transformation; at the other end, hereditary sensitization of the tissues is so intense that ordinary metabolic changes or slightly abnormal ones, such as would be innocuous in an ordinary individual, can lead to the production of cancer. Midway between these two extremes we find all kinds of quantitatively varying combinations.

Secondly, cancer in this respect does not differ from a large number of other diseases, in which we also find such varying combinations between hereditary and environmental factors.

During the process of transition from a normal to a cancer cell, the former acquires step by step some new properties, as far as structure, metabolism, proliferation and ameboid activity, chemical constitution, and transplantability are concerned. Above all, to emphasize the essential point, the cell assumes an increased proliferative activity, and often an increased ameboid activity; it penetrates into the surrounding tissue, is carried away by the blood or lymph stream and produces metastases in different places.

If we transplant cancer cells from one individual into other individuals of the same species and strain, it is possible, in the case of a certain number of tumors, to make them grow in the strange hosts and to transplant them

indefinitely from generation to generation into other organisms of the same strain. However, in the case of other tumors, such transplantation does not succeed; the cells behave like normal tissue cells and can be transplanted only into the animal in which they originated. Between these two extremes all kinds of intermediate conditions exist. In transferring those tumors which can be readily transplanted, we quite commonly notice that a gradual increase in growth energy takes place in the course of the first transplantations; even through ordinary mechanical stimuli the growth can be increased. Similarly through the use of certain injurious factors the growth energy can be depressed. In experiments carried out with M. S. Fleisher, we could furthermore show that it is possible to a certain extent, to immunize cancer cells against the effect of certain substances and that this change is transmitted to subsequent cell generations.

The transplantability of tumor cells from generation to generation proves that they are potentially immortal; but inasmuch as they are merely transformed tissue cells the tissue cells themselves from which they originated are also potentially immortal, a conclusion which has been confirmed by long-continued growth of fibroblasts in tissue culture. Not in the potential immortality, therefore, do tumor cells differ from ordinary tissue cells, but they differ from the latter in their constant excessive activity and in their resistance to the toxic factors active in homoiotransplantations, to which normal cells succumb.

In this connection I might emphasize once more the great importance of

transplantation as a method in tumor investigation. Transplantation is not merely an imitation of metastasis formation as is occasionally stated. Metastases are autotransplantations occurring under uncontrolled conditions. Transplantations can be defined as homoiometastases produced at will, experimentally, under controlled conditions. This method is indispensable in tumor investigations. It makes possible not only the study of the specific character of tumor cells, but it is necessary also as an instrument in the analysis of the character of the cancerous transformation.

By means of this method there was discovered one of the most important effects of cancerous growth, namely, that of stimulating other tissues with which the cancer cells are in contact also to become cancerous. Such a contact action is not an exceptional occurrence. Strange as this effect may appear, related growth-promoting contact substances are normally given off by the so called organizers which play such an important rôle during embryonic development<sup>6</sup>; even during adult life such substances regulate the interaction of tissues and according to their character either stimulate or inhibit growth phenomena.

Should it not be possible to extract experimentally these growth promoting contact substances directly from tumor cells and transfer them separately from the latter into other individuals and thus produce cancer? Our first experiments in this direction with a rat sarcoma were unsuccessful. While filtrates through filter paper, which did not hold back the cells, produced tumors, filtrates through Berkefeld filters



did not. A number of years later Peyton Rous showed that in the case of sarcomata found in chickens, cell-free filtrates injected into other chickens gave rise to similar sarcomata. This proved to be an extremely important finding, which, apparently, depended not on the transfer of a living filterable microorganism but on that of a chemical substance inciting growth.

There is, therefore, no doubt that, in certain cases, agents distinct and separate from tumor cells can produce a cancerous transformation of normal cells. Subsequently the attempt has been made to effect a similar separation of an agent from tumor cells in the case of various mammalian cancers. While we cannot deny that it may be possible to accomplish such a result, it seems to me that a definite proof of it has not yet been given. It appears, furthermore, that also in the case of the experimentally produced tumors in fowl, in which certain investigators believed they had demonstrated the presence of such an agent distinct from cells, the actual proof still awaits confirmation.

While thus, as far as we can see at present, the existence of a separate agent causing tumor formation has been demonstrated with certainty only under two conditions, namely, in the case of the contact cancerous transformation and in the chicken sarcomata, we must consider it probable that similar organizer-like substances are active also in the case of other tumors and that perhaps future methods of research will establish their existence.

In tissue cultures, A. Fischer and his associates have observed that cancer cells, while they may not grow more rapidly than normal regenerating cells,

have the power to outgrow the latter in the end and usually to destroy them.

The injurious action exerted by cancer cells, under these conditions, is probably due to abnormal products of metabolism given off by tumor cells or to abnormal enzymes. Such an abnormal metabolism of cancer cells has been discovered in recent years by Warburg and it has been found also in tumors growing in the living animal by Cori. In tumor cells, as in yeast cells, the enzymatic splitting of carbohydrates and the production of lactic acid by this means is very marked, not only under anaerobic but under aerobic conditions as well. Although these findings are of great interest and importance, still they do not absolutely differentiate cancerous from normal tissues. In particular regenerating tissue approaches in this as well as in other respects cancer very closely, even more so than does embryonic tissue. Again we notice that no sharp line of demarcation exists between normal and cancerous tissues.

There is, however, an interesting set of phenomena, which seem to point to a somewhat greater difference between malignant tumors and normal cells, namely, their behavior in immunity. As we have stated above, cancers, like normal tissues, can almost invariably be transplanted into the same organism (auto-transplantation). In a number of cases they can be transplanted also into other individuals of the same strain. This may be due partly to their increased proliferative activity, but probably also to a change in their individuality or organismal differential, that which differentiates the various organisms from each other<sup>e</sup>. In addition, a



change in the organ differential, which differentiates the various tissues and organs within the same organism, may be involved. The latter conclusions are based mainly on three lines of evidence, namely, (1) On the fact stated above, that many tumors, in contradistinction to normal tissues, can readily be transplanted into other animals of the same species and that from generation to generation of cancer cells the excessive cell activity persists. (2) On the experiments of Lumsden, who believes he has been able to differentiate between that type of immunity against transplanted (homoio) tumors which is directed against substances which these tumors have in common with other cells of the same organism and species, and the type of immunity which is directed against substances which all cancers have in common and which is independent of individual and species differentials. Therefore, tumor cells must differ in their chemical constitution from normal cells of the organism in which they have developed. (3) On experiments by Hirszfeld, Witebsky and Lehmann-Facijs, who found, in cancer, antigens of a lipoid character; and in this case, also, according to the latter investigator, these antigens are of two kinds, namely, those bearing the organismal and others bearing the organ differential. It seems furthermore that, in cancer cells, antigens originate which have certain constituents in common with the heterogenetic antigens.

These observations seem to sustain a suggestion made by Tyzzer and the writer many years ago, namely, that cancer growth may be conceived of as due to a somatic mutation, which signifies a change in the gene constitution of

a few localized cells; this mutation would explain the persistence of the characteristics which tissue cells assume when they become transformed into tumor cells. Such a somatic mutation is to be distinguished from a germinal mutation, which latter affects the germ cells and is responsible for hereditary changes in the organism as a whole and is transmitted from generation to generation of organisms. In harmony with the assumption of somatic mutation are also the recent experiments of L. C. Strong, who found that two tumors originating in the same mouse and, therefore, originally endowed with the same individuality differential, behaved differently from each other in the course of transplantation into the same types of hosts and in particular did they show a different behavior according to the sex of the host.

There is some reason for assuming that such an acquired difference in the organ and organismal differentials of certain localized tissues may alter their relationship to the neighboring tissues. The normally existing restraining contact substances of an autogenous character may not function typically towards abnormal tissues and the affected tissues may be uninfluenced by the normal regulating and restraining hormones; these disconnected tissues would thus grow as a more or less independent organism within an organism. This circumstance together with the other acquired characteristics, in particular the increased growth energy of cancer and the changed metabolism, would explain the peculiar behavior of cancer cells. With this change would go hand in hand a more active production of growth promoting substances, which

would constantly renew themselves inside the proliferating cells and spur on the latter to continued excess activity under abnormal conditions. It appears as if the activity of these cells automatically leads to the new production of such substances; and thus we would have to deal with processes autocatalytic in their action. Furthermore, it seems that in certain cases such substances can be extracted from the cancer cells and exert their effect on neighboring tissues.

While transplantation and other methods give us an insight into the distinctive features of cancer and normal cells and into the changes which take place in normal cells during cancerous transformation, they do not furnish us directly with an understanding of the factors which bring about this transformation. In this we have to deal with an entirely different problem and we have shown that here hereditary factors in combination with various growth-promoting agencies play the main rôle. But in this case the hereditary factors concern the germ cells and the genes located there, and furthermore germ cell mutations may perhaps be responsible for the hereditary predisposition to cancerous transformation. Both the germ cell changes as well as the somatic changes are hereditary, but each in a different way and each must be studied by different methods. If we interpret, tentatively at present, the action of heredity as sensitizing the substratum to the effect of various growth promoting agencies, then we may conclude that all the factors which cause cancer have in common that they increase the proliferative activity of cells usually over a long period of time and we may

conclude that it is this continued excess in proliferative activity in localized and often in sensitized cells which leads in the end to the cancerous transformation.

I cannot close without discussing briefly the possible significance of micro-organisms in the etiology of cancer. Recent investigations have not tended to lend support to the view that micro-organisms may be the essential cause of this condition—a cause which acts perhaps in combination with other factors, as Gye and Barnard assumed. On the whole, the repetition of Gye's experiments by other investigators has not confirmed the facts on which this assumption is based. Neither do other claims in this respect seem to be much better founded. If micro-organisms should play a part in the etiology of cancer, this part is probably none other than that played by higher parasites, such as spiroptera of Fibiger, in the case of carcinoma of the forestomach of rats, and the *cysticercus crassicolis* with which Bullock produced sarcoma in the liver of rats. These parasites apparently give off substances which stimulate the surrounding tissue cells to undergo cancerous transformation. But they are not concerned in the growth of cancer cells as such; and they do not, as far as we know at present, provide the constant stimulus which spurs on the formerly normal cells to grow as cancer cells continuously, and without which the cancerous tissue would resume a normal growth. The bacteria present in the crown gall of certain plants may perhaps play such a stimulating rôle, but there does not exist convincing evidence of a similar

kind in the case of mammalian and in particular of human tumors.

It might be possible to think of the chicken sarcoma agent, or of the agent that causes the development of contact cancers—as when a sarcoma develops in contact with a carcinoma—as filterable micro-organisms, but what we know of the character of the chicken sarcoma agent fits in as well, or even better, with the idea that it represents a complex organic substance, presumably of a colloid nature.

In view of all the other data, which we possess, as to the etiology of cancer, the theory which I have presented in this paper seems to me much more probable, at the present time, than the assumption that, in the cases mentioned, a living micro-organism is transferred. What we know of the rôle of extraneous growth substances, and of internal secretions, in the etiology of cancer, and of their interaction with heredity, all these well established facts do not seem very well compatible with the assumption that micro-organisms are the essential cause of cancer, and that cancer is therefore merely a peculiar type of an infectious disease. Furthermore, what we know of the behavior of transplanted tumors and of immunity in cancer, does not lend support to that view.

All these facts are compatible, however, with the conception that certain growth stimuli acting in association with hereditary factors, which latter may perhaps sensitize the cells to the action of the growth stimuli, cause a gradual transformation of normal into cancerous cells. During this process the

cells step by step assume characteristics which are very similar to those which regenerating cells possess, but these characteristics are even more accentuated in the case of cancer cells than in the case of ordinary regenerating cells. Whereas in the case of regenerating cells these changes are temporary—the cells soon returning to the equilibrium of normal tissue—in the case of cancer these properties, once acquired, are permanent. The mechanisms underlying these properties are constantly reproduced within the cells thus affected, and are transmitted to succeeding generations indefinitely. This transformation leads to a new state of cell equilibrium which potentially exists in all cells which have the ability to proliferate. In the course of this transformation, certain changes of a delicate nature take place in the chemical constitution of the cells; the transformation seems, to a limited extent, to affect those chemical processes on which the individuality and tissue differentials depend, and inasmuch as we have to deal with a definite change transmitted in the same way from cell to cell generation, we may assume that the fixed cell constituents, which determine these biochemical properties, are permanently altered. We may, therefore, conceive of this process as a somatic mutation, a mutation occurring in certain ordinary tissue cells. At the same time, we must assume that the proneness to undergo this somatic mutation depends largely, but not entirely, upon the genetic constitution which these somatic cells received from the germ cells.

## The Influence of Heredity on the Occurrence of Cancer in Animals\*

By H. GIDEON WELLS, *Chicago, Illinois*

**I**N order to keep within the time limit I propose to present my material in the form of a brief synopsis to be followed by a series of lantern slides which will serve to illustrate some of the points I hope to make.

The justification of speaking on the subject of cancer in animals before a group of men interested in human medicine lies in the fact that it would seem that our best prospect of obtaining reliable information concerning the influence that heredity may play in the occurrence of cancer will come through the study of cancer in animals. All hereditary studies in man are difficult because of the long period between generations, the small families, and uncertainties of diagnosis. To be sure, we can learn and have learned some things concerning the relation of heredity to the occurrence of cancer in man, and Dr. Warthin will speak of these.

To get the matter under adequately controlled conditions so that we can repeat our observations and verify them, it becomes necessary to study the disease in animals.

Before we can utilize the returns of

this sort of procedure, we have to establish certain facts: First, that cancer in animals is the same disease that it is in man; and, second, that the rules of heredity are the same in animals as in man.

In the beginning of our studies of experimental cancer, much doubt was thrown on the proposition that the disease that we were studying in animals was identical with human cancer. There are certain differences to be observed between different species in respect to incidence and behavior of cancer, but as we have learned more and more concerning animal cancer, these doubts have been dispelled, so that it is now safe to say, I think, that there is no reasonable doubt that fundamentally cancer is the same in all species of animals, although differences occur between different species.

In the other matter, as to the identity of the laws of heredity in man and animals, we have only to recall the fact that the principle of genetic transmission of character was discovered by Mendel, working with plants; that these principles, lost for thirty-five years, were rediscovered by botanists working with plants; that immediately the zoologists took up the matter they found that in all species of animals to

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\*Presented in the Symposium on Cancer before the American College of Physicians, Minneapolis, Feb. 13, 1930.

which they applied these principles the laws were found to be the same, and that we have no reason to suppose that what holds for all other multicellular living forms will not hold for man. As a matter of fact, we all know that certain conditions are inherited in man exactly as other conditions are inherited in animals; for example, the classical case of color blindness which obeys very definitely the Mendelian principles.

The study of the influence of heredity on the occurrence of cancer in animals may be carried out in several ways, one in a broad way, is by comparative pathology. There are very distinct differences in the occurrences of different sorts of cancer in different species. Why should different species behave differently? They are different species through heredity, of course, and the fact that in swine a common tumor is a mixed tumor of the kidney, that in sheep primary epithelial tumors of the liver seem to be particularly common, that in mice mammary gland tumors are particularly common, in rats the usual growths are sarcomas, illustrates hereditary differences in species in respect to the occurrence of cancer.

To me, particularly striking is the domestic cow. In most mammals one of the commonest site for the occurrence of tumors is the mammary gland. Of all species of mammals there is none in which the mammary gland is subjected to so much over-stimulation, abuse, traumatism, and so on, as the dairy cow, and yet there are practically no cases, so far as I know only two cases have ever been described, of cancer in the mammary gland of cows. That sort of thing is related to the well known

human fact that fibroid tumors of the uterus seem to be particularly frequent in the negro, and there are other instances that might be cited.

The experimental study of the relation of heredity to cancer in animals can be carried out in two ways: One by the study of transplanted tumors. Thirty years ago Dr. Loeb and Dr. Jensen contributed a great deal to cancer research by their discovery of the possibility of series transplantations of cancers. We have learned much about cancer through that method. But in regard to heredity, it does not seem to offer us so much, for the reason that the principles that determine whether a transplanted cancer will grow in another animal from the one which furnished the original cells seems to be something entirely different from the principles that determine that a given animal will develop a cancer from its own cells, and it has been found experimentally that the behavior from the genetic standpoint of transplanted cancer is very different from the behavior of spontaneous cancers.

The other way is to study the occurrence of cancers arising spontaneously in the ordinary course of the animal's life, or cancers produced by stimulation with tar or other means. These things come nearer the human problem and are being studied zealously in many places.

At the present time we cannot present a complete picture of how heredity does modify the development of spontaneous cancers in animals, but this much has been established, and I think is pretty generally agreed: that the study of experimental animals has shown beyond any question of doubt



that heredity does play a very great rôle in determining not only whether animals will or will not develop cancer, but where they will develop it, that is in what organ, and also the type. For example, certain strains of mice produce cancers almost exclusively in the mammary gland, but it is possible to find strains of mice in which the tumor is predominantly in the lung, and to produce strains of mice in which the tumor is predominantly a sarcoma arising at the point of injury. That seems to be adequately established.

It also is established that heredity may determine whether cancer will or will not arise from a fairly constant type of injury. For example, in Dr. Wood's laboratory the demonstration that the infestation of the liver of rats with certain parasites leads to sarcoma, was followed by the demonstration that certain strains of rats would show this condition very much more frequently than other strains which seemed to be relatively immune from the development of malignant tumor, although their livers were equally infested with parasites.

So these things add up to what Dr. Loeb has already told you, that the combination of the genetic background and the stimulation are together the essential things. In fact, I think that was expressed best years ago by Dr. Loeb himself, in this very simple equation: that cancer is the product of heredity by stimulation. It is perfectly evident in this simple equation that you can get the same end result, whether the heredity factor is large and the stimulation small or the stimulation large and the heredity factor small.  $H \times S = C$ .

It is a question, perhaps, whether the hereditary resistance to cancer is ever so great that it will resist all attempts at production of cancer, but certainly there are cases where the heredity factor is so large that any ordinary amount of stimulation such as occurs in ordinary life without obvious injury may fail to result in cancer. On the other hand, the inherited lack of resistance to cancer may be so marked that cancer occurs with a minimum of antecedent injury. I might refer to gliomas in man, which occur early in life, not the result of any obvious trauma, but apparently entirely determined by heredity.

Those are the main points, or as much as I can give you in the time at my disposal. I should like to show a few slides to illustrate some of these points.

First of all, the fact that cancer is the same thing in animals as in man. Here, for example, is a carcinoma of the stomach in a mouse. That brings up another difference due possibly to heredity, or possibly to other factors in the production of cancer, that man is the only species in whom cancer of the stomach is not the greatest of rarities, whereas in man we all know it ranks first. This is one of the few known cases of glandular carcinoma of the stomach in the mouse, and it is in structure quite the same thing as carcinoma of the stomach in a man, you see.

The animal cancer that has been most studied in laboratories is the mammary gland cancer of mice. Here is shown a cancer developing in a lactating mammary gland. If you compare the normal lactating mammary gland with the carcinoma, you see it shows about the same sort of differences you are accus-



tomed to seeing in human mammary cancer. They behave in all respects the same.

Here is a mouse carcinoma invading the wall of a blood vessel, producing a tumor thrombus from which emboli may escape to other parts; for example here in the lung is a tumor embolus. Certain strains of mice will develop secondary tumors in the lung, and others will not irrespective of whether the emboli go there or not. In certain strains the emboli go there and die; in other strains they multiply and you find the lung filled with tumor metastases, as here. In other words, the behavior in respect to metastases and all that is the same in these animals as in man.

Here are metastases of a mammary gland cancer occurring in the liver of a mouse. You see the same picture that you are familiar with in human cancers. Again, here is seen a tumor metastasis from a cancer of the lung of a mouse involving a bone and leading to a pathological fracture. Also we see mouse cancers invading a lymph node, passing through the lymphatics as do human cancers.

Not only do the carcinomas occur in the mammary gland of these mice, but they occur elsewhere in the same sort of way. For example, here are sections from a mouse that had an ulcer following a wound of the skin. Then on that ulcer, just as might happen in an ulcer in a man, is seen a squamous cell carcinoma that has invaded and is spreading beneath the overlying skin, to illustrate that cancers occur under the same conditions in mice and man.

This mouse had a broken tooth which irritated the mucous membrane, and here is seen the squamous cell car-

cinoma of the mouth that developed. In this case it has invaded the base of the skull and is producing pressure on the central nervous system, just as such a carcinoma might do in a man.

Here are sections from another mouse that had a prolapsed rectum for a long time, and in that prolapsed rectum first occurred epithelial metaplasia, and then this condition, carcinoma.

Mice have basal cell carcinoma, as shown in the next slides, so-called rodent ulcer type of carcinoma. The interesting thing is that they are so identical with the behavior in human species that they are seen chiefly in very old mice. This picture shows an extremely old mouse that had his face eaten away by basal cell carcinoma. Histologically these growths present the same character as in man, and also the same character of not tending to produce metastases.

Not only do these animals have carcinomas, but they have sarcomas. Here is a round cell sarcoma of a mouse. You see it is quite the same picture as a human round cell sarcoma, and the next few slides illustrate the fact that mice have the various histological types of sarcoma seen in man.

Also benign tumors occur. For example, here is an adenoma of the ovary of a mouse, and here are uterine fibroids. In fact, I have seen in mice nearly every tumor that I have ever seen in the human species, with few exceptions. So then we have to admit that tumors are essentially quite the same in all species.

As I have said, the transplanted tumors in mice are different in many respects from the spontaneous tumors. One essential difference is that many

transplanted tumors will grow for a time and disappear spontaneously, differing fundamentally from spontaneous tumors in this respect. Whether a transplanted tumor will take or not depends upon something about the reaction of the individual to foreign cells, a factor that is not present in the spontaneous tumors. Consequently, it is not strange that we have found that the study of transplanted tumors shows them to obey different laws from the spontaneous tumors.

Our great hope, I think, lies in the new developments that have come through the work of Yamagiwa in producing carcinomas in animals by irritation of the skin by tar. It thus becomes possible to produce at will cancers in animals from their own cells, analogous to cancers arising in man, and to study the hereditary influences. This work is new, but much probably will come of it.

I cannot go into the details of the mechanisms by which heredity determines the occurrence of cancer. That is not yet agreed upon. Miss Slye, with her large material, has observed in her experience that susceptibility to cancer behaves as a Mendelian recessive, and that resistance is dominant. Other workers are not ready to accept this view and present evidence which they interpret to the contrary, so we will have to consider that this subject is still unsettled. The important fact now available is that it seems to be fully established that heredity does play a large rôle in determining whether an animal will have a cancer or not, and what sort of a cancer it is likely to be.

Miss Slye has shown that it is possible to produce from mice with cancer, bred with non-cancerous mice, different

strains, some of which will show cancer and others not. She has produced strains like this that have gone for twenty-five or thirty generations with never a cancer in them, whereas other offspring of the same original mating produced cancer regularly. But more important for the human problem, is her production of strains in which the cancer crops out after intervals of several generations. For example, in the chart here shown, are several intervening generations without cancer, but it appears again, and then it disappears. This behavior is entirely analogous to what is observed with recessive inheritable qualities generally. This sort of thing Miss Slye interprets as indicating that cancer behaves as a recessive character.

There are other illustrations of similar behavior of neoplasm. For example, Miss Stark, working with a fruit fly, has produced a type of fruit fly in which a growth resembling a melanotic tumor appears in one half of the male larvae, and in this behavior it shows susceptibility as a recessive, as Miss Slye's work with the mice indicates.

We seem justified in saying that the study of heredity in cancer will probably have to be carried on largely with animal material, from which we may hope to learn how to understand the things we already have observed and will observe in the future in regard to the relation of heredity to cancer in man. A good start has been made. So far the main result of the work is, as I see it, to settle beyond question that heredity does play an important rôle. The ways in which the heredity brings about the susceptibility or resistance to cancer remain to be determined.

## Hereditry of Carcinoma in Man\*

By ALDRED SCOTT WARTHIN, *Ann Arbor, Michigan*

IF one may judge from the literature, all of the animal experimental work on the heredity of cancer susceptibility has not made a very deep impression on the general medical mind, because in very few textbooks on pathology and special works on cancer, and in the propaganda literature of associations for the prevention or control of cancer, very little, if any, emphasis is laid upon the part played by heredity in the etiology of neoplasms. As far as our present statistics concerning the heredity of cancer in man are concerned, I believe that they have very little value indeed. No statistical problem offers greater difficulties than that of the incidence of family susceptibility to cancer in the general population. The average hospital case-histories throw but little light on this question; even in specialized teaching hospitals in which the taking of clinical histories is supposed to be more or less supervised from a teaching standpoint, the histories of individual cases of cancer usually contain no information as to the multiple incidence of cancer in the families of the cancer patients. During the years 1907-1909 I collected from the histories of the Surgical Department of the University Hospital what

data I could find relating to the multiple incidence of neoplasm in the families of patients who had been operated upon for carcinoma. In the ordinary run of case histories from the surgical clinic, it was found that less than one per cent of such cases gave any family history of cancer at all. When, however, these same cases were investigated by a special method, in the form of letters or personal communications with the family of the patient, this percentage was raised to over fifty per cent.

The bald question, directed to the patient himself as to the occurrence of other cases of cancer in his family, is very often unproductive of positive information. The affected individual has very frequently about the same attitude towards revealing any family history of carcinoma that he has towards giving any history of syphilitic infection, or of the inevitable sexual phenomena of old age. Many have a certain horror or a fear of the stigma attaching to a family history of multiple incidence of neoplasm. Moreover, there are relatively few individuals in the average hospital population who know their own family history back of the immediate parental generation. It is a very great mistake to depend upon the patient himself for the essentials of a family history. Other members of the

\*Presented in the Symposium on Cancer before the American College of Physicians, February 13, 1930.

family should be questioned. Further, very few hospitals pay sufficient attention to the importance of having the interne make special inquiry as to multiple family incidence of neoplasm. The importance of the constitution and of hereditary susceptibility is not yet recognized by the average practitioner or medical teacher of today; and this fact is reflected in the inadequate case-histories made by the average interne. In addition to the imperfections of history-taking, cancer statistics are further vitiated by the great frequency of both positive and negative incorrect diagnoses.

The first slides shown present examples of the multiple incidence of cancer in the families of carcinoma patients operated in the University Hospital prior to 1908, and represent the results of special investigation made to ascertain the occurrence of multiple cancers in the families of given patients. It will be seen that as a rule not more than three generations are represented. Some of these family histories are incomplete in so far as they do not include all of the non-cancerous members of the family. Moreover, some of the "cancers" of the first generation represent family tradition only, the organ or tissue specifically involved not being known. A collection of such histories showing the multiple familial occurrence of cancer was published in a paper by me on "Heredity with Reference to Carcinoma" in the *Archives of Internal Medicine*, 1913. There were 330 cases included in this investigation and over 50 per cent showed a multiple incidence of carcinoma in different generations. In the remaining 50 per cent of cases in which a history of multiple

incidence could not be obtained, this failure was due almost wholly to the ignorance of the patient or other member of his family concerning his family history as far as the cause of death of the various members was concerned. That a positive history of multiple incidence of neoplasm in the same family could be obtained in 50 per cent of cases by means of special investigation speaks strongly in favor of an hereditary family susceptibility.

These collected examples of multiple familial incidence of cancer showed a number of interesting things. In some families the carcinoma cases appeared in every generation, indicating a direct inheritance. In other families the cases of cancer may skip a generation, or even two, the cancer-cases appearing in the collateral lines, and not in the direct line for one or two generations. To the generations showing multiple occurrence of cancer cases I applied the name, cancer fraternities or cancer generations. The collected charts show that carcinoma may be passed on through the direct line, or through the collateral lines, and may appear in every generation, or may skip one or two generations. (See Fig. 1.)

In certain families the incidence of carcinoma becomes so marked, the cases so crowded, that these can be properly designated as cancer families. For instance, one family shows two cases in the first generation, four in the second, and two in the fourth, the incidence being so great as to stigmatize this family as a "cancer family." In this family the maternal grandmother died of "tumor." Her non-cancerous brother had two children both of whom died of "tumor." Her son married a woman

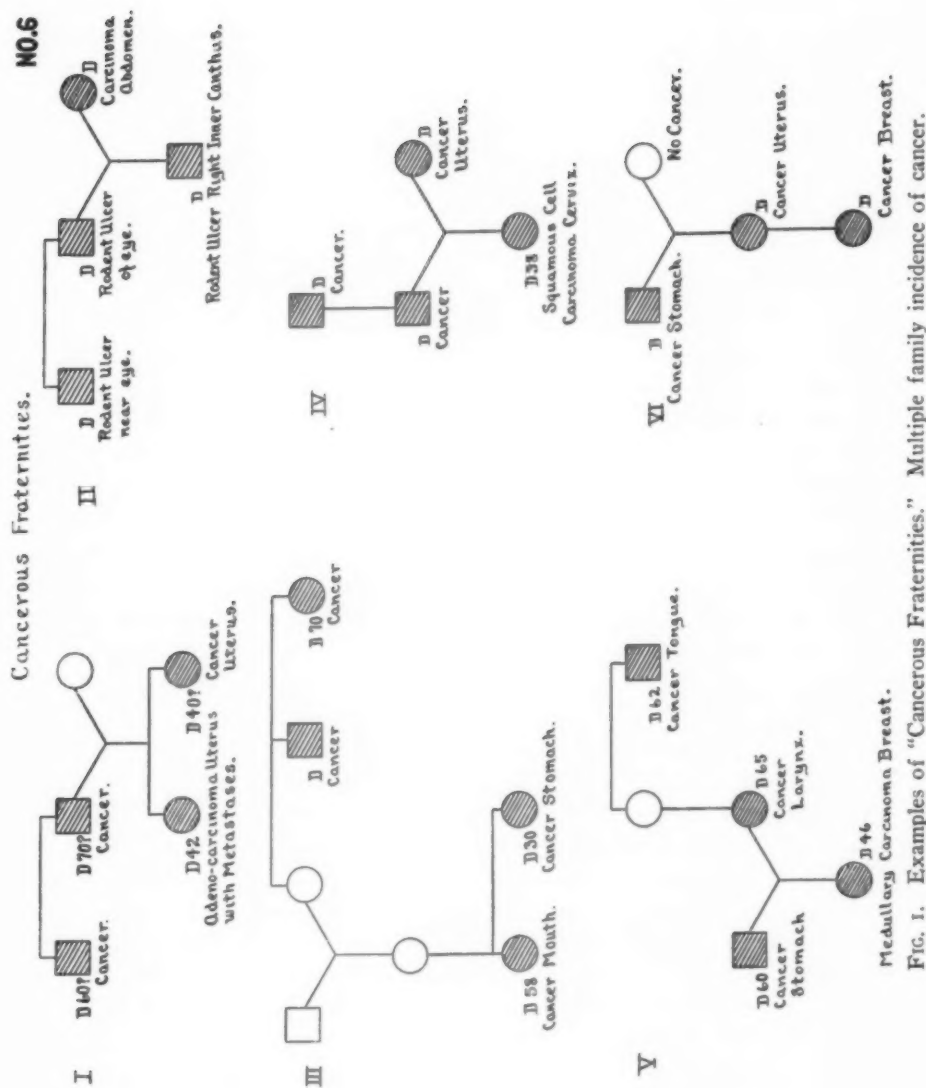


FIG. 1. Examples of "Cancerous Fraternities." Multiple family incidence of cancer.



who had two brothers die of cancer of the stomach. Neither the son or his wife developed cancer, but they had only three children, daughters, who all died of malignant tumors, in two cases of the uterus, and in one case of the ovary. In Family O (Fig. 2) the collateral transmission of cancer is well shown. In Family P (Fig. 3) there were 8 cases of carcinoma in three generations, the inheritance being both collateral and direct. In the third generation of 13 children, three daughters died at relatively early ages of cancer of the breast, while 5 brothers and 5 sisters died of tuberculosis before the age of thirty. This association of a family susceptibility to tuberculosis with that to carcinoma we have repeatedly noticed in our material. In Figs. 4 and 5 other examples of this association are shown.

Since 1913 this laboratory has collected a large number of family records showing the multiple incidence of neoplasm. One fact stands out very prominently in these records, and that is the tendency for the carcinoma to be localized in certain organs or systems, as for example, the gastro-intestinal tract or the sexual organs. In a given family the affected males may show carcinomas of the gastro-intestinal tract and the females carcinomas of the sexual organs, particularly breast and uterus. There is apparently a local *organ* or *tissue susceptibility* inherited. In Family S (Fig. 6) the great grandfather died of cancer of the stomach. His son also died of cancer of the stomach after marrying a woman who died of cancer of the breast. They had six children, all of them dying of cancer; three daughters of cancer of the breast, two sons of

cancer of the stomach, and another son dying of abdominal cancer not precisely located. The youngest son married a woman without a family history of cancer. They had one child, a daughter, dying at 36 of cancer of the uterus. In Fig. 7 the predominance of cancer localized in the sexual organs is shown. This inheritance of a local predisposition to neoplasm is especially marked in the case of the so-called glioma of the retina (retinoblastoma). The observation of Purtscher (Fig. 8) is an example illustrating this point. From a grandfather who had sarcoma of the arm, there were 11 children, three of who had retinal glioma. From one of these gliomatous daughters, there came a son with glioma; and from another normal daughter there came two gliomatous sons. Instances are recorded of some of the glioma families in which all of the children have been affected. In one family there were 13 cases of glioma in two generations, and in another 18 cases in three generations.

In some families a distinct inheritance of two organ susceptibilities has been observed, as for example, cancer of the respiratory tract and cancer of the genito-urinary organs. Very frequently this local organ predisposition to cancer shows a sex-limited inheritance. In Fig. 9, the family chart shows a predilection of cancer for the larynx in the males, and for the breast in the females.

In 1913 I reported the study of a German family living in Washtenaw County, Michigan, in which up to that time there had occurred 18 cases of carcinoma in three generations (see Fig. 10). In 1925 I made a more complete study of the same family (*Jour.*



# CANCER FAMILY O

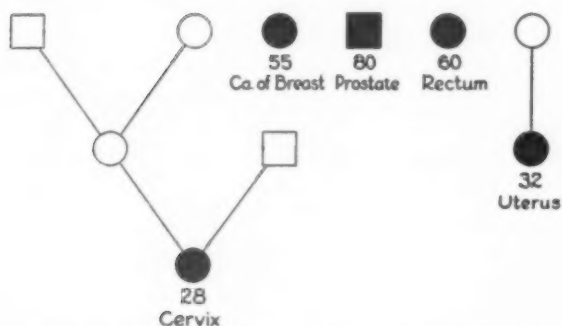


FIG. 2. Multiple family incidence of cancer in the collateral lines.

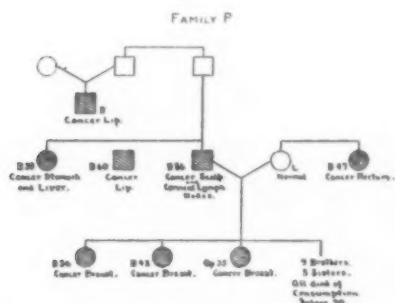


FIG. 3. Multiple family incidence of cancer. Two local predispositions shown: Gastro-intestinal tract and breast. Also the associated susceptibility to tuberculosis.

# CANCER AND TUBERCULOSIS FAMILY

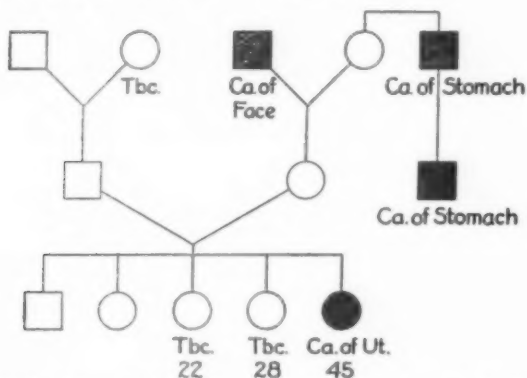


FIG. 4. Family history showing association of cancer and tuberculosis.

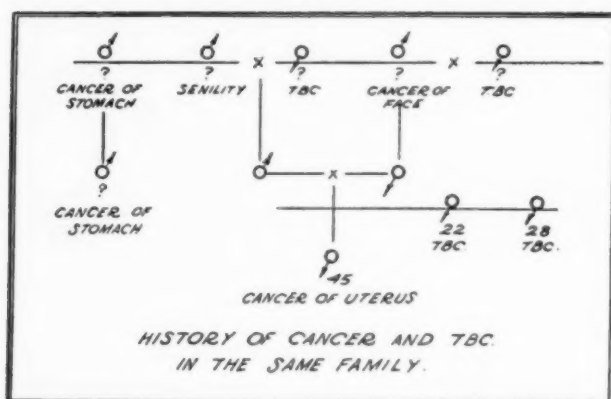


FIG. 5. Family history of associated cancer and tuberculosis.

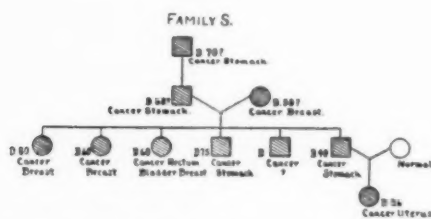


FIG. 6. Example of "Durchschlag" inheritance of cancer. Also two system predispositions: Gastro-intestinal tract and sexual organs.

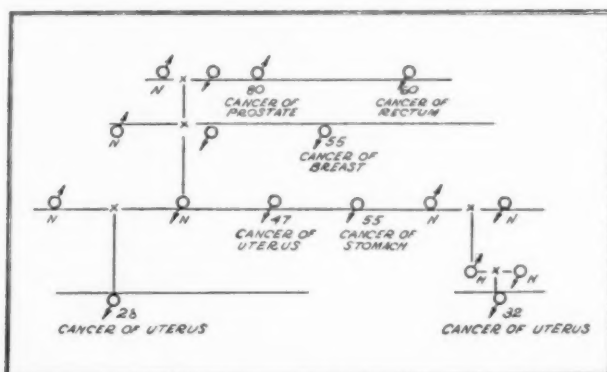


FIG. 7. Example of two system predispositions to cancer: Sexual organs and gastro-intestinal tract.

of *Cancer Research*, Vol. IX, 1925), giving a full list of all the members of the family, with corrected age-orders, both cancerous and unaffected individuals. In the chart made at this time (see Fig. 11) there were 28 cases of cancer out of a total of 146 individuals comprising the family, an incidence of 31.81 per cent of cancer in the 88 adult members of the family. Since the second report in 1925, ten more deaths from cancer have taken place in this family, an incidence of 43.2 per cent in the adult members of the family. The first known occurrence of cancer was that of the great-grandfather who died

at the age of 50 with cancer of stomach or intestine. This family represents such a widespread distribution of cancer susceptibility in its members, that there is a possibility that every member might die of cancer if he lived long enough. To such a marked family susceptibility to cancer, Bauer, in a personal communication, has applied the term "Durchschlag." This same family shows also an associated predisposition to tuberculosis. A marked local organ predilection is also shown in this family; in the males carcinoma of the intestines and stomach predominate; in the females carcinoma of the uterus. Orig-

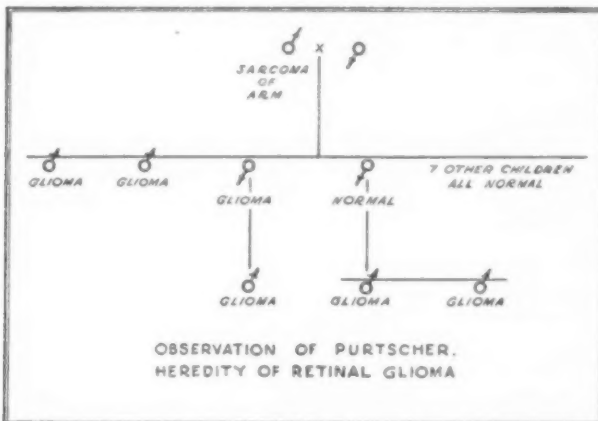


FIG. 8. Heredity of retinal glioma. Multiple family incidence.

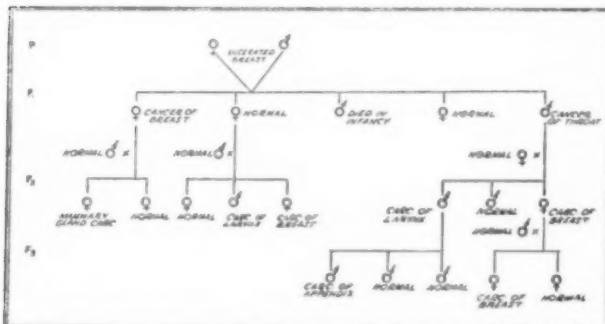


FIG. 9. Family history of predisposition to cancer of respiratory tract in males, of breast in females.

inally regarded as an example of recessive heredity of the carcinoma factor, it is much more probable that the inheritance in this family is dominant, inasmuch as the cancer cases all come from cancer parents. It is also of note that as far as could be ascertained, none of the individuals who married into this family had a family history of cancer.

The family shown in Fig. 6 is another example of "Durchschlag" family inheritance of cancer susceptibility. A great-grandfather died at 70 of cancer of the stomach. His wife had no family history of cancer. His son died in the forties of cancer, after marrying a woman who died in the fifties of cancer of the breast. They had three daughters and three sons, all of whom

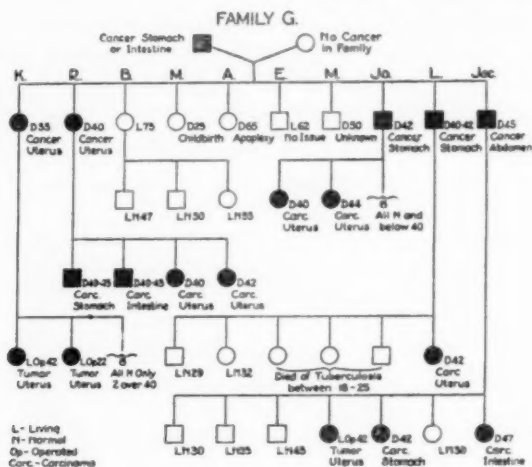


FIG. 10. Family history of "Durchschlag" inheritance of cancer, in 1913. Eighteen deaths from cancer.

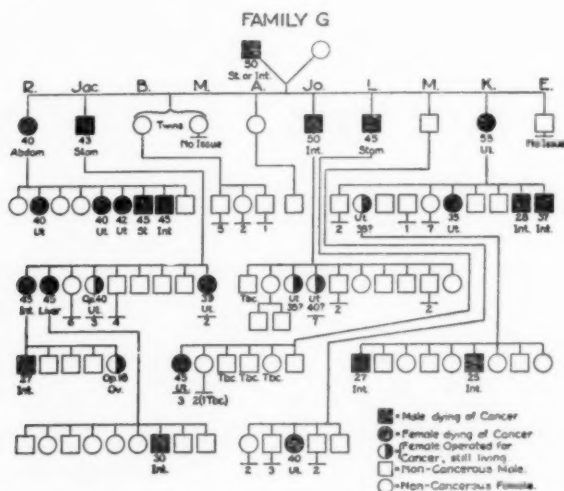


FIG. 11. Chart of same family as preceding, made in 1925. Twenty-eight deaths from cancer. Since this last chart ten more deaths from cancer have occurred in this family.

died of cancer. One son married a woman without any history of family cancer, and their only child died at 36 of cancer of the uterus. The other members of the third generation were childless; the family terminated its line with the cancerous great-granddaughter.

In all families showing a "Durchschlag" tendency it is important to note the fact that the carcinoma develops at an earlier age in the later generations, so early in some instances that the individual is under the age of 30, a minimal cancer age according to some authorities. Apparently there is a progressive inheritance of the carcinoma susceptibility in some members of these families leading to a development of the

carcinoma independently of the action of any extrinsic factor.

Others of our histories show very interesting things. In some families there is a very marked variation in cancer susceptibility in the different members of the family. In Fig. 12 is a chart of a family in which for two previous generations the male members died of smoker's cancer of the lip. In the present generation there were four sons, three of whom died of smoker's cancer of the lip between the ages of 40-45. The fourth son who did not smoke lived to the age of 63, when he too died of carcinoma of the lip, arising apparently independently of the extrinsic factor. This would appear to be a carcinoma wholly intrinsic in nature. Fig.

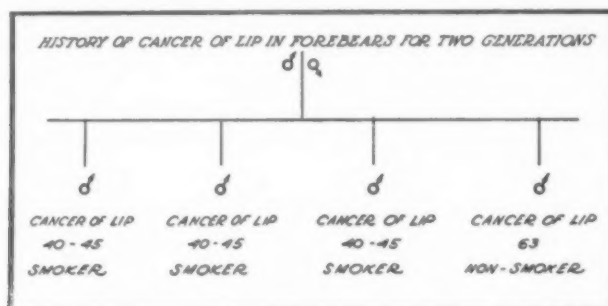


FIG. 12. Chart of family showing marked predisposition to "smoker's cancer" in middle life. One member, a non-smoker, developed same cancer of lip at 63 years.

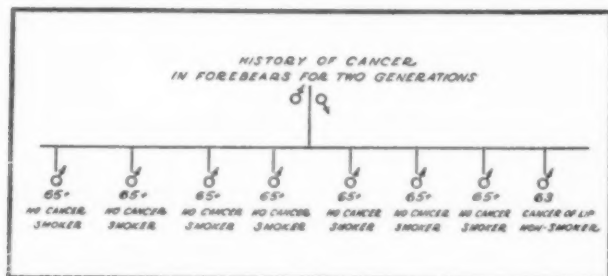


FIG. 13. Chart of family with history of "smoker's cancer" for two generations, with seven members of third generation, all smokers, but free from lip cancer, while the eighth, a non-smoker, develops carcinoma of the lip.

13 tells a story quite different in its possible interpretation. As in the previous family, the two previous generations showed smoker's cancer of the lip in the male members. In the present generation there were eight sons, seven of whom were smokers and lived over 65 years without developing cancer of the lip, while the eighth son, a non-smoker, died at 63 of cancer of the lip. The cancer-susceptibility which showed in him alone developed purely intrinsically, without the aid of the extrinsic factor. Contradictory as such histories may appear to be on the surface, yet they are also explainable on the grounds of constitutional susceptibility to cancer, and a local predisposition independent of any apparent extrinsic factor.

As to the question of dominance or recessiveness of the carcinoma factor in human families, there would appear to be in some families a dominant inheritance, in others a recessive inheritance of the cancer factor. The great variation in susceptibility found in different members of the same family may possibly be explained by the great complexity of the cancer character. It cannot be a single simple Mendelian character, but may consist of a combination of a large number of factors. Moreover, we are not sure that the inheritance of the cancer-susceptibility in man is always Mendelian. From the available evidence we are sure of two things: a constitutional susceptibility to neoplasm, and a local organ-predisposition to cancer. The first determines that a man may develop cancer; the second determines the organ or tissue involved.

The existence of a constitutional susceptibility to neoplasm and of a lo-

cal organ-predisposition is particularly shown in the case of the gastro-intestinal tract. The studies of Bauer and Aschner, Spiegel, and others, have shown that there is a familial stomach-predisposition showing itself as chronic dyspepsia, particularly of the nervous type, ulcer of the stomach, or gastric cancer. In the study of 255 ulcer patients and 400 normal individuals made by Bauer and Aschner, the incidence of cancer of the stomach in the families of ulcer cases is not greater than 19.83 per cent and not less than 7.63. The minimal value is twice as great as the incidence of gastric cancer in the families of 400 normal controls. Spiegel, in a study of 121 ulcer patients and 200 normal individuals, found that every 6-7th ulcer patient showed carcinoma of the stomach in his family history, while in the non-ulcer individuals only every 40th had a family history of carcinoma. The high incidence of carcinoma of the stomach in the family histories of gastric ulcer cases points to the important rôle played by constitutional organ-predisposition in the origin of gastric ulcer and gastric cancer. When both the constitutional susceptibility to cancer and the local stomach predisposition are present in the same individual, then gastric ulcer may be the local predisposing factor to cancer development. As a matter of fact the development of cancer in a chronic peptic ulcer of stomach or duodenum is but rarely seen; so that if a patient has ulcer he is pretty likely to escape cancer, or is more likely to have it in other parts of the body than in the stomach. In a recent autopsy in my service, a woman with three chronic peptic ulcers of the stomach developed



what is relatively rare in women, a primary carcinoma of the esophagus. It would seem, therefore, that an inferior stomach-constitution in itself does not necessarily predispose to cancer. There must be both a general blastoma susceptibility and a local organ predisposition to cancer present in the individual who develops cancer.

Another important fact in proof of the hereditary nature of cancer susceptibility is the occurrence of symmetrical neoplasms in members of the same family. The slide shows large symmetrical xanthomas of both elbows in two sisters. If our theory is correct that constitutional predisposition and organ predisposition to cancer are necessary to the development of a cancer, we should expect to find in identical twins, examples of neoplasms affecting the same organ and the same part of the same organ. And this is precisely what has been observed in a number of cases. In one case reported by me, malignant teratomas of the ovary developed in each of identical twin sisters. In one case the ovary involved was a mirror image of the ovary affected in the other. We have seen also symmetrical adenofibromas of the breast becoming malignant in identical twins. Symmetrical malignant teratomas of the testes have also been reported in identical male twins. Such occurrences can be

interpreted only as proof of the hereditary nature of cancer susceptibility and local organ predisposition.

Putting all of the observed facts together, as shown by this rapid and incomplete survey, we possess the following data concerning hereditary susceptibility to neoplasm: multiple incidence of neoplasm in family generations; dominant inheritance of neoplasm in some families; recessive inheritance of neoplasm in some families; "Durchschlag" inheritance in some families; appearance of neoplasm at an early age in the later generations; appearance of neoplasm independently of extrinsic factors; multiple incidence of neoplasm affecting the same organ or system; multiple incidence of neoplasm affecting different organs or systems; varying degrees of resistance or susceptibility to neoplasm within the same family generation; symmetrical tumors in different members of the family; and the occurrence of symmetrical neoplasms in the same organ and part of the organ or its mirror image in identical twins.

It seems to the writer that the best interpretation of these facts rests upon the assumption of at least four hereditary factors: the normal constitution resistant to blastoma; the pathologic blastoma constitution; the normal resistant organ or tissue make-up; and

#### FACTS CONCERNING INHERITED NEOPLASM SUSCEPTIBILITY

1. Multiple Incidence of Neoplasm in Family Generations.
2. Dominant Inheritance of Neoplasm in Some Families.
3. Recessive Inheritance of Neoplasm in Some Families.
4. Sex-limited Inheritance of Neoplasm in Some Families.
5. "Durchschlag" Inheritance of Neoplasm in Some Families.
6. Appearance of Neoplasm Independently of Extrinsic Factors.
7. Appearance of Neoplasm at Early Age.
8. Multiple Incidence of Neoplasm Affecting Same Organ or System.
9. Resistance or Non-Susceptibility to Neoplasm in Some Families.
10. Different Degrees of Susceptibility in the Same Family.

FIG. 14. Summary of the facts known about inheritance of tumor susceptibility.

the pathologic organ predisposition to cancer. Each of these factors must be composite; no one is a simple unit factor in the Mendelian sense. Each one represents large and complex genes in which a hundred or a thousand subsidiary factors may enter and which may mendelize independently or in combination. The old conceptions of dominant and recessive have lost their original significance as far as the inheritance of neoplasm in man is concerned. The possibilities of inheritance in the almost endless combinations that may result, the effect of diluent or intensifying combinations, the occurrence of lethal factors and their combinations, the action of the extrinsic factors of the environment, and other modifying factors make the problem of the inheritance of carcinoma in man one beyond mathematical computation or prediction. The conception of Mendelism which led Maud Slye to regard the inheritable tumor susceptibility as a simple recessive unit character is all too primitive. Characters that show a dominant inheritance in several generations may be so modified that they hereafter show a recessive inheritance. Theoretically the laws of Mendel have added much to our understanding of heredity, but their practical application in human heredity is limited because of the complexity of the problem.

Nevertheless, in some families the four factors mentioned above appear to be inherited as genes. If *B* represents the normal constitution, *b* the blastoma predisposition, *O* the normal organ, and *o* the organ predisposition, the possibilities of the heredity of cancer susceptibility would be expressed in Figs. 15, 16, 17, and 18. If *B* is dominant

over *b*, and *O* over *o*, there would be out of nine genetic possibilities, only one cancer candidate, that is, one homozygote recessive *bb.oo*, No. 9. But if *b* and *o* are dominant, the individuals, 5, 6, 8, and 9 will be cancer candidates. If *b* is dominant over *B*, and *O* over *o*, only the individuals represented by 6 and 9 would be cancer candidates. The blastoma predisposition of the constitution must be very much more widespread in the community than the number of cancer deaths would indicate because many individuals die before reaching the cancer age. Only in those families in which a definite organ predisposition, *oo*, is present, will the blastoma anlage, *b* or *bb*, assert itself.

The familial occurrence of carcinoma depends in the first place upon the wide distribution of the blastoma constitution, and secondly upon the occurrence of the organ predisposition. If *b* is dominant, then 75 per cent in the first familial generation may expect to be carcinomatous. If *b* is recessive, 100 per cent in the first family generation may show it. If an individual has a father who dies of cancer of the stomach and a mother who dies of cancer of the thyroid, there is no greater chance of the children developing neoplasm than if just one parent has a neoplasm. But should the family history for several generations back show other cases of cancer of the thyroid and of the stomach, then the chances for carcinoma of either thyroid or stomach, or of both organs, are much greater in the progeny. If one parent possesses both pathologic organ predispositions in stomach and thyroid in homozygote form, *bb.ss.tt*, which may not manifest

## THEORY OF CONSTITUTIONAL CANCER SUSCEPTIBILITY

- B* Normal Constitution  
*b* Blastoma Predisposition  
*O* Normal Organ  
*o* Organ Predisposition

*Hereditary Structure as to Cancer Predisposition Expressed in Usual Formula would be*

1. *BB·OO*, 2. *BB·Oo*, 3. *BB·oo*, 4. *Bb·OO*, 5. *Bb·Oo*, 6. *Bb·oo*, 7. *bb·OO*, 8. *bb·Oo*, 9. *bb·oo*.

If *B* is dominant over *b* and *O* over *o*, there would be out of the 9 possibilities only 1 Cancer Candidate, the homozygote recessive *bb·oo*, No. 9.

If *b* and *o* are dominant the individuals 5, 6, 8 and 9 will be predisposed to cancer since they possess both pathological hereditary factors as heterozygote or homozygote.

If *b* is dominant over *B* and *O* over *o*, only the individuals represented by 6 and 9 would show a cancer predisposition.

FIG. 15.

If 10 per cent of the population die of cancer, the pathologic blastoma-predisposition *b* must be widely distributed individually; if *b* is dominant much more than in one-tenth of the population; if recessive more than  $\frac{1}{\sqrt{10}}$  or  $\frac{1}{3.16}$ . In the first case more than every tenth person would possess *b*; in the second case more than every third would possess it either in simple or heterozygote form. The constitutional blastoma predisposition must be much more extensively distributed than the cancer mortality, since many cancer candidates die of other diseases and escape their constitutional fate. Only in those families in which a definite organ-predisposition *oo* is present, will the blastoma anlage, *b* or *bb*, assert itself.

FIG. 16.

*The familial occurrence of carcinoma depends upon the wide distribution of  $b$  in the first place, and secondly upon the occurrence of the organ-predisposition  $oo$ .*

*If  $b$  is dominant:*

$$\begin{array}{rcl} \frac{Bb \cdot oo \times Bb \cdot oo}{BB \cdot oo} & . . . . . & P \\ 2 Bb \cdot oo \left\{ \begin{array}{l} 75 \text{ per cent.} \end{array} \right. & . . . & F_1 \\ bb \cdot oo \end{array}$$

*If  $b$  is recessive:*

$$\begin{array}{rcl} \frac{bb \cdot oo \times bb \cdot oo}{bb \cdot oo} & . . . . . & P \\ & 100 \text{ per cent.} & F_1 \end{array}$$

FIG. 17.

*If both parents die of carcinoma of different organs (as stomach cancer,  $ss$ , thyroid cancer,  $tt$ ) the chances for the children are not much worse than in the case of one cancerous parent.*

*Stomach cancer  $\times$  Thyroid cancer*

$$\begin{array}{rcl} \frac{bb \cdot ss \cdot TT \times bb \cdot SS \cdot tt}{bb \cdot Ss \cdot Tt} & . . . . . & P \\ & & F_1 \end{array}$$

*If these parents possess no other organ-predisposition, the children would remain cancer-free. If the pathologic organ-predisposition leading to cancer in one parent is present in heterozygote form in the other, 50 per cent of the children would be cancerous. When  $b$  is dominant the number would be reduced to  $\frac{3}{8}$ , 37.50 per cent.*

$$\begin{array}{rcl} \frac{bb \cdot ss \cdot TT \times bb \cdot Ss \cdot tt}{bb \cdot Ss \cdot Tt} & . . . . . & P \\ & & F_1 \\ Bb \cdot ss \cdot Tt & (50 \text{ per cent stomach cancer}) \end{array}$$

FIG. 18.

itself in the phenotype because he dies of carcinoma of one organ, 100 per cent, relatively 75 per cent, of cancerous children may be expected. The hereditary biologic formula in this case is the same as that of multiple primary carcinoma of different organs.

As to the relation of extrinsic factors to the intrinsic, very little is known. Can an extrinsic factor take the place of the intrinsic organ predisposition, and create a local predisposition? Many workers hold that this is so, but the absence of an intrinsic local predisposing factor cannot be positively proved in any human case. We see, at least, great variations in the potency of the extrinsic factor in the case of different members of the same family. In some, the neoplasm may develop so early in life that the extrinsic factor may be excluded; in some the cancer develops at the cancer age either independently of the extrinsic factor, or dependent upon the latter; other members of the family may reach extreme old age and develop cancer either independently of the extrinsic factor or dependent upon it. Some individuals with intrinsic constitution require an intensive action of the extrinsic factor to bring about the development of cancer.

Some writers on this subject hold that both the constitutional and the local organ predisposition to cancer may be acquired, or one inherited and the other acquired. They explain the occurrence of x-ray cancer, paraffin cancer, arsenic cancer, mineral oil cancers, tar cancers, Bilharzia carcinoma, Kangri cancer, and carcinomas arising in old scars, as the result of an acquired perversion of regenerative processes. It is not so easy to exclude the exist-

ence of an inherited factor in any of these cases, and the question as to the purely acquired character of the origin of the cancer must still be kept open.

The local organ or tissue predisposition can be recognized in many cases as an embryonal anlage, associated with disturbances of development. To such developmental disturbances we refer the malignant teratomas of ovary and testis, the malignant neuroblastoma of the retina and sympathetic system, the malignant neoplasms of the adrenals and kidneys in the newborn, the malignant hypernephromas and carcinomas of the kidneys in the adult, branchiogenic carcinomas, familial intestinal polyposis, chordoma, angiomas, and numerous others. Cohnheim's theory of tumor etiology has received a new value in recent years; developmental disturbances are the chief morphological evidences of local tumor-predisposition. At least they are the forms recognizable by our present technical methods. In all of these developmental disturbances there is a strong factor of heredity, and some writers dispose of the question of heredity of neoplasm by the assumption that it is the disturbance of development which alone is inherited, and not the susceptibility to cancer. These writers, therefore, hold that carcinoma inheritance is dependent wholly upon the inheritance of malformations or abnormal developmental anlage. This view is not in accord with the actual facts observed. It is true that constitutional and local predisposition to cancer may in themselves be the result of abnormal development, but these writers do not regard it in that sense. Further, may not an inherited tendency to abnormal regeneration in



response to the extrinsic factor be the thing that lies behind the etiology of these supposed acquired forms of cancer?

As far as the practical application of the points brought out in this paper are concerned, the individual who has a single case of cancer developing in two or three generations of his family has not great cause for worry. But the individual who has a family history of the multiple incidence of cancer in several generations should take heed. Particularly important is the investigation of the collateral lines with reference to multiple incidence of cancer, rather than in the line of direct descent. Such an individual with a history of the multiple familial incidence of cancer should avoid all of the known extrinsic agents associated with the etiology of cancer. Chronic irritation of any form that may lead to abnormal regeneration should be removed or obviated. He should not smoke; he should not engage in any industry in which mineral

oil, tar, paraffin, or other irritating products that might lead to the production of cancer, are used. He should not expose himself to irradiation. Scars of the skin, particularly large scars from burns, should be treated by skin grafting. All developmental anomalies should be corrected or removed. Rough pigmented moles should be removed. All chronic inflammatory conditions occurring in such an individual should be healed as quickly as possible.

Finally, there is the question of breeding as a general preventive measure. The man who has a history of the multiple incidence of carcinoma in his family should not marry a woman who has the same kind of a family history, but he should marry a woman who has no history of cancer in her family. It is but rational and logical to apply preventive measures of eugenics to this problem; and till such measures are considered as practical, there can be no great hope for any speedy conquest of this great plague of mankind.



## The Principles of Radiation Treatment\*

By FRANCIS CARTER WOOD, M.D., *New York*

THE relation of bacteria to disease was a mystery until Pasteur and Koch developed culture media which permitted the isolation of the pathogenic from the host of contaminating organisms present in the body and allowed the study of its characteristics in pure culture and facilitated the demonstration on animals of its special qualities. So all broad advances in the understanding of the principles underlying the action of radiation will only be gained by using the same method, that of experiment. Experiment consists only in simplifying conditions of observation so that confusing elements are as far as possible eliminated. The term radiation includes all forms of atomic energy transmissible through a vacuum. The discussion will be confined to a limited region of radiation employed practically, that of the gamma and x-rays, the wave lengths of which are so short that the effects are atomic and not molecular. Ultraviolet light, ordinary visible light, and long wave length heat are therefore excluded from consideration. The study of the biological action of any radiation presumes that we are able to define with considerable accuracy the wave

length of such an agent and its intensity. This is now true for x-rays and the gamma rays of radium, though as yet it has not been possible to measure radium radiation accurately in terms of the international r unit for x-ray.

Assuming these quantitative factors as determinable, it is then necessary to study the action of the rays to learn, if possible, the minute changes in cells or other substances under investigation which follow radiation, and lastly to observe the effect of such changes upon the complex living organism as a whole. At first in order to avoid complications such an organism must be as simple as possible, either a free swimming creature like a protozoon, the eggs of marine animals, like *Arbacia*, the normal habitat of which is sea-water, or minute eggs such as those of the *Ascaris megalocephala*, or insect eggs, of which the most convenient type is that of the fruit-fly, *Drosophila*. The radiation of whole animals or of growing plants introduces so many factors which are not always easy to control that they are not satisfactory for investigations of the laws of biological action. The effects of radiation on considerable amounts of tissue are so complex that their study belongs rather to the clinical aspect of the question and is often a matter purely of statistical observation and does not permit of any unravelling

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of the finer principles. The difficulty in obtaining approximately normal growth of animal tumor cells or even of normal tissues has prevented the general use of such material in studying the biological effects of radiation.

A. The influence of physical factors upon the biological action of radiation. The first physical factor which has to be investigated in order to observe the biological action of radiation is that of wave length, and those wave lengths are chosen arbitrarily as the regions which are used in practice. This includes all rays whose wave lengths is from 2 ångströms, the so-called long wave length x-rays or the Grenz rays, up to the short waves of radium or mesothorium, many of which lie on the short side of 0.01 ångström. This limitation excludes the characteristic x-radiation from some of the lighter substances which are largely absorbed in a few centimeters of air, and of course also excludes ultra-violet and other types of light. Within the limits given the wave length of the radiation seems to play no part, provided the measurements are made with an open ionization chamber, using air at the normal temperatures and pressures as the medium ionized. While physically the short wave lengths carry more energy than the long, this is compensated in the chamber by their lack of absorption. The absorption in such a chamber of 10 or 15 cm. length is approximately the same as the absorption in the minute biological objects mentioned above. Most physicists and many biologists have long held that it was self-evident that the only effect produced in a cell by radiation is parallel with the absorption of energy;

in other words, that if the absorption in the ionization chamber and the absorption in tissues were the same, the biological results should be the same, and this the experiments of Wood and Prime and Packard at the Institute of Cancer Research, Columbia University, have shown to be true, for under these conditions of measurement, using a continuous x-ray beam; the biological effects on isolated cells or small aggregates of cells are independent of the wave length. Each cell in the tissues of the human patient must therefore be affected independently of the wave length of the radiation which reaches it. To reach cells deeply placed penetrating wave lengths must be used, for surface tissues longer wave lengths can be used. Whether or not the open ionization chamber measures energy makes no difference in these experiments, because the amount of energy absorbed in the column of air is about the same as that absorbed in the material exposed. In order to parallel the conditions existing both in the chamber and in the radiated tissue, the latter must be of small dimensions and suspended in the air upon thin gauze so that there can be no question of any secondary radiation affecting the amount of x-ray received by the individual cell by "scatter" from surrounding objects. The measurement of the gamma rays of radium cannot be accomplished by an open ionization chamber with any accuracy as yet, so that strictly quantitative comparisons between x-ray and radium have not been made, but the curves of the lethal action of such radiation and also of the Bucky rays exactly superimpose, provided that the 50 per cent. point is used to adjust the

position of the curve on the horizontal axis. The laws governing the lethal action must therefore be the same. The x-ray and radium measurements, however, can be made at present within a moderate percentage error by comparison of erythema doses and by using various measuring chambers, so that the differences can scarcely be more than 10 or 15 per cent. It is therefore probable that when gamma rays can be determined in r units they will be found to be quantitatively equal to the short wave length x-rays, though the final proof has not been brought. But the rate of killing of *Drosophila* eggs is exactly the same with equal quantities of the two radiations as it is with the longer of 2 ångstrom units. Hence the sum of the effects of any two wave lengths will be the same as an equal quantity of one wave length, always remembering that this applies to individual cells, and not to large quantities of tissue. The effect on a cell 10 centimeters below the surface of the skin of two half skin erythemas, one with Bucky rays, the other with radium gamma rays will not be the same as if one erythema was given with gamma rays, because much less radiation will reach the cell in the first instance as compared to the last. These results have been confirmed by Holthusen and others on a variety of biological material. Recently Morse and Fricke have shown that the rate of decomposition of hemoglobin and aqueous solutions of ferrous salts was likewise independent of wave length, so that it has been shown that this law is true of animal tumors, of *Drosophila* eggs, and of solutions. The discordant results which have been published by Russ, Dognon

and other workers are probably due to some error in technique. Thus the old statement of Krönig and Friedrich, published in 1918, is confirmed, though it has been pointed out that their results were only accidentally correct, because the dimensions of the ionization chamber which they used happened to give measurements which were independent of the wave lengths used.

B. The influence of the time and quantity relationships of radiation are not so fully determined. Wood and Prime showed that on animal tumors a threshold existed with radium below which no biological effect took place; in other words, the cells could repair the damage as rapidly as they were injured. Packard has shown that the same is true of *Drosophila* eggs with x-ray. But above this point Krönig and Friedrich demonstrated that no difference could be observed when the dose was diminished by one-fifth and given over five times the time, in other words, the product of the intensity by the time was a constant. Hence within certain time limits biologic material can be employed to measure the intensity of radiation. Wood and Prime showed this also for tumor particles with x-ray and radium at ratios of one to eight, and Packard has shown that the law holds with *Drosophila* eggs, but it is difficult with all this experimental material to extend the time factor much more than one to eight, as most of the tissues used cannot be preserved for more than four or five hours without undergoing such deterioration as to interfere with the accuracy of the test. Further studies which have been made are chiefly those of Regaud and his colleagues, which have been made upon

the testicles of rams. They showed that long-continued small doses are more effective than short high intensity doses. But in these experiments there were complications brought in by the very complexity of the reactions which they regarded as indicating their end-point. The same is true of the radiation of plants or of tumors growing in the host. It is not possible to eliminate completely the interplay of other factors which may increase or diminish the effectiveness of the radiation. The general feeling, however, from the clinical point of view is that the prolongation of radiation over a very considerable time permits more effective treatment with less damage to the normal tissues than a large dose given in a short time. Certain animal tumor experiments carried out under Regaud's auspices point in this direction also, but the work needs to be rechecked with a large number of different tumors before it is safe to make any generalizations.

C. The physical and chemical actions which underlie the biological effects of radiation.—The nature of the physical actions which take place in tissues when they are rayed by short wave lengths can only be guessed at at the present time. The passage of such radiation through the tissues may be assumed to set free electrons but this assumption is based wholly upon the demonstration by Wilson of the freeing of such electrons in a gas by x-rays or gamma rays and rendering them visible by the condensation of moisture upon them during their flight. The instantaneous photographs show that the velocity of an electron increases with decreasing wave length, and that such secondary electrons occasionally strike

other atoms and set up secondary radiations either of the same wave length, of a slightly smaller wave length, or a very much longer wave length, the latter being due to the production of the characteristic radiations of elements of low atomic weight. The demonstration of these very long wave lengths has been obtained by photographing their spectra in a vacuum as they are completely absorbed by air. The atom is also capable of scattering rays of the same wave length as the impinging beam and also rays of longer wave lengths. (The Compton effect.) Each of these different types of rays is capable of giving rise to fresh electrons. The assumption is generally made that the action of radiation is due to such electrons. It is certain that a pure electron beam may cause the death of cells. This was first shown by Exner many years ago, who exposed cells to a beam of electrons deflected from a radium source by means of an electro-magnet. Recent experiments which have followed the development by Coolidge of a tube which gives a beam of electrons in the open air have shown the highly destructive effects on tissues of such electron showers. Penetration of course is very slight because these electrons themselves are stopped by a few inches of air. Whether the radiation itself has any direct effect is doubtful, for even in studying the photographic effect of gamma or short wave length x-rays the experiments lead to the belief that it is an electron phenomenon in the silver halide which makes the image developable. The effect of such short wave length radiation cannot be referred to direct heat for the amount of heat set free by a beam of x-rays is so small

that it can be scarcely measured. Dessauer has suggested, however, that active molecular actions may be set up either by the rays or by the stopping of electrons and that these vibrations are equivalent to an enormous quantity of heat set free at one point, and that this heat may, for example, start small coagulation centers in the protein molecule. An attempt has been made by one of Dessauer's pupils to demonstrate such points of coagulation by studying protein solutions with a dark field illuminator, and it has been observed that there is an increase in the number of small visible particles in such a solution after radiation, but after longer exposure the number decreased again. The experiment must be tried on inorganic colloids in which coagulation can not take place before this result can be accepted as sustaining Dessauer's viewpoint. It is possible also that the setting free of electrons changes the electrical charge of the atoms of the tissue, and this induces chemical changes. It is certain that the action of intense radiation over a long time will decompose water, setting free hydrogen, and that such an effect might result in damage to the protein molecule, but as yet this is all pure speculation. In a gross sense protein solutions can be so altered that they coagulate easily; changes have been observed in the viscosity of protein solutions after radiation, and various protein suspensions have revealed visible precipitation after prolonged exposure. The radiation of hemoglobin produces also alteration in the molecule of that substance. The surface tension of serum is altered by heavy radiation, and its reaction is changed toward the acid side. Lipoids

are also altered. But all of these results are obtained only with enormous doses of radiation, hundreds of times those required to kill living cells, and while they suggest processes which may go on in such a cell, they do not prove that such alterations underlie the lethal action.

One of the most interesting phenomena has been observed on the eggs of *Arbacia* and protozoa, that the permeability of the cell membrane, as tested by vital stains, is greatly increased by very moderate exposures, and that as the cell regenerates and regains its original condition, the absorbed dye is again extruded.

*The latent period.*—The raying of dead tissue reveals no morphological changes. Living cells show no immediate change, even after considerable radiation. This latent period varies a good deal with the biological material and with the dose, the larger the dose, the shorter the latent period. As previously stated, a threshold dose is always necessary to produce noticeable changes. The cells can regenerate after a certain amount of exposure and apparently return to a perfectly normal condition. When the dose exceeds this threshold and after a considerable period, scarcely ever less than 24 hours, morphological changes begin to make their appearance. They are noticed chiefly in the nuclei, in the form of breaking up of chromosomes into fine, dust-like particles; obliteration of the nuclear membrane, and swelling of the cell, which appears glassy, and ultimately in the formation of syncytial masses. These are all familiar to those who study tumors after radiation. Canti has photographed these changes



in tumor cells growing in culture. It is evident that the nuclei are extremely sensitive, as was long ago observed by Perthes on the eggs of *Ascaris*. Later stages show changes in the cell protoplasm, in alterations in its reaction to dyes, and especially the absorption of vital dyes, in the tinctorial properties of connective tissue and other fibrils. But these changes are by no means specific of radiation. They may be produced equally well by suitable chemicals or by the action of other physical agents, such as heat or cold.

*Functional alterations.*—Certain functional changes may also be noticed in the cells. They become less actively ameboid. They may lose their phagocytic qualities, and the functions of the cells of certain complex tissues, like glands, may be sufficiently altered to give clinical symptoms. The dangerous toxic reactions which are produced after excessive radiations of the thyroid in exophthalmic goiter, or the active flooding which follows the radiation of the ovaries in a patient with menorrhagia are two interesting clinical phenomena. In animals the stimulation of the salivary and other glands has been demonstrated, excessive doses causing a diminution in function. Rapidly dividing cells are more affected than those which do not divide. Hence the tissues of the brain are insensitive, and as Prime has shown, and Rosso has later confirmed, the radiation of the beating heart muscle cell in culture may cause no alteration in the function of the cell, though the dose is far beyond that required to kill connective tissue cells growing under the same circumstances, but actively dividing. Evidently radiation, though seriously damaging

the nucleus and ultimately causing the death of the cell by such damage, does not interfere with the metabolism of carbohydrates sufficiently to stop the muscular contractions.

The radiation of cancer and also normal material in culture often requires large doses to accomplish the lethal effect. If such cells are immediately transplanted to fresh media after radiation they may continue to grow under a suitable dosage. If left in the medium for a suitable time they will not grow. This can be interpreted in two ways, one that there is some toxic substance generated in the medium either by the direct action of the radiation or by the excretion of metabolic products from the injured cells. The other is that such cells can "make the grade" only if supplied with fresh food. The same is observable with animal tumors. If they are radiated and immediately transplanted, growth will take place. If they are left for a considerable time before grafting, no tumor results. This is easily explicable on the basis that not only were the radiation effects developing in the cells under conditions which do not permit of regeneration, but that the grafting process causes additional trauma, and that the cells when they are grafted are not capable of obtaining sufficient nourishment to enable them to go on and grow. The assumption has been made that the tissues elaborate toxic substances after radiation which destroy the cells, but there are two experiments which make this very doubtful. The first was reported by Jüngling who rayed the chest of a patient under a grid-like filter, so that an area of 2 or 3 mm. was exposed to



radiation, and a similar adjacent area received no radiation. The tumor receded only in the exposed strips, showing that this hypothetical tissue reaction did not extend even a couple of millimeters. The second experiment was that of Wood, who showed that the dose required to destroy the tumor cells was the same, whether the tumor was rayed in the animal, or exposed *in vitro* and then inoculated. That the circulation contains a cell poison after radiation is negated by transfusion experiments from rayed animals to those bearing tumors. No effect is produced.

*Immunity to radiation.*—The action of the rays has also been supposed to cause the tumor cells to become resistant, a so-called radiation immunity. The observation is unquestionable, as tumors which have been rayed for a long time cannot be as effectively treated by renewed radiation as those which have never been exposed. Here again other factors appear. One of the effects of radiation, and an extremely important one, is damage to the terminal arterioles. This consists of swelling of the endothelium, of edema and vacuolization of the sub-intimal tissues, and of the muscular coats, so that the vessel in exceptional circumstances may be completely closed or be filled by a thrombus. This obviously cuts off food from the tumor cells, and causes the clinical appearance of the destruction of the growth. When the cells start to grow again, it is impossible to give to such damaged tissues the same amount of radiation, because they are badly nourished. The vessels having once been closed, no clinical effect can be obtained by radiation, for there is no longer any means of diminishing the blood supply

to the growing cancer cells. That any change occurs in the tumor cells themselves owing to repeated radiations has been disproved by Prime, who rayed a highly virulent animal tumor and then transplanted it. This process was repeated many times, and at the termination of the experiment, no difference in the lethal dose of radiation was found as compared to an unrayed tumor. The same is true after raying the tumor in the animal with sublethal doses, then comparing the killing dose with that of previously unrayed tumors. It is evident that a simpler explanation than that of some immunity must be sought. The one given above seems to be the most probable.

*Sensitivity to radiation.*—The sensitivity of tissues, both *in vitro* and *in vivo*, varies considerably. The resistance of the brain cells to heavy radiation has already been mentioned. Endothelium and the walls of the vessels are much more sensitive. The tissues of the bone marrow are extremely sensitive. On the other hand, radiation of the circulating blood shows that the blood cells are resistant after they have once reached their development. Certain of the connective tissues resist successfully enormous quantities of radiation. The tissues of the kidney and adrenal are rather sensitive. What underlies these biological differences is impossible to state at the present time. Wood and Prime have shown that different animal tumors of similar types require different dosages, and the same observation was later made upon human tumors. The morphology of the tissues is not necessarily a guide to their radio-sensitivity. One tumor may be sensitive, whereas a tumor of exactly the

same morphology may be resistant. Such biological phenomena escape our analysis at the present moment.

#### CONCLUSIONS

I. The action of radiation is in all probability due to the secondary effect of free electrons released by the action of the rays on the atomic structures of the tissues.

II. The effect on the individual cell is independent of the wave length.

III. The effect on large masses of tissues is dependent on the wave length in that the intensity of the radiation at any given depth is a function of the

wave length and the scattering of the rays in the tissues.

IV. The effect is twofold, primarily a direct one on the cells, and a secondary nutritional damage due to vascular injury. No proof is yet available of a tissue toxicity as a factor in cell destruction.

V. There is no evidence of a cellular immunity following radiation.

VI. Cells vary greatly in their sensitivity to radiation for reasons as yet unknown.

VII. The ultimate evaluation of the therapeutic possibilities of radiation rests on clinical observation.

# Spontaneous Pneumothorax\*

## A Discussion of Its Causes

By FRANK J. HIRSCHBOECK, *The Duluth Clinic, Duluth, Minn.*

**B**Y "spontaneous pneumothorax" I mean to indicate all pneumothoraces which are not induced by external factors, either accidental or for therapeutic purposes. In the literature one finds that some writers limit the term spontaneous pneumothorax to those instances in which the etiology is not demonstrable by our clinical examination, but I believe that these might be more properly classified as the idiopathic type of spontaneous pneumothorax in order to avoid confusion. The distinction in classifying this group separately is of importance, because of certain specific characteristics in the idiopathic cases.

Spontaneous pneumothorax occurs most often between the ages of 15 to 45; according to Nikolsky<sup>1</sup> in 80 per cent of the cases. Males are affected more often than females, in the proportion of 4 to 1. This is usually explained on the basis of increased effort and strain in the male. It is said to occur with equal frequency on both sides of the chest, though individual statistics vary on this point.

Spontaneous pneumothorax may be multilocular or unilocular, depending on pleural limitation; partial or total;

unilateral or bilateral; simple or complicated with effusion, and may be recurrent. In the bilateral cases, of which about 15 have been reported in the literature, death does not necessarily ensue, as one might surmise, as 4 of the series have recovered.

Spontaneous pneumothorax has also been classified clinically into certain types. The pneumothoracic cavity may be of the closed type, meaning thereby a sealing up of the communication between the pleural cavity and the pulmonary tissue; open, if a free communication exists between the pleura and the pulmonary fistula; or of the valvular type if a check-valve action is developed, either because of the valvular nature of the opening or because of a fibrinous flap. As a result on inspiration air more or less freely enters the pleural cavity, but is not effectively expelled during expiration, resulting in a gradual increase in the intrathoracic pressure on the affected side, usually with the development of serious dyspnea, cyanosis, mediastinal shifting and circulatory embarrassment. These latter symptoms serve to distinguish the more serious valvular type from the others, but the diagnosis of this type can be further established by the introduction of a needle connected with the manom-

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eter tube of a pneumothorax apparatus. It is observed that in the closed type the manometric pressure decreases with inspiration and increases with expiration; in the open type the manometric reading remains at zero, whereas in the valvular type the positive pressure is greatly increased and may be as high as 10 to 14+ instead of the normal -2 to -5.

It has long been known that pulmonary tuberculosis is the most frequent cause of spontaneous pneumothorax, but that it is an almost universal cause, as is oftentimes intimated, must be denied.

The most elaborate statistics on the etiology available in the literature up to the present time are those often quoted from Biach<sup>2</sup>, based on 38 years' experience in 3 Vienna hospitals. It was found that in his series of 918 cases, 715 were due to pulmonary tuberculosis—an average of 77 per cent. The next most frequent cause was gangrene of the lung, with 65 instances, many of which were probably associated with pneumonia; empyema rupturing into the lung with 45 cases, and injury with 32. Other causes of lesser importance and frequency were rupture of the lung from bronchiectasis, pulmonary abscess, emphysema, infarction, paracentesis, perforation from adjacent air-containing organs, bone caries, and a group of 14 instances in which the cause was not ascertained.

One can learn from these statistics that the etiology varies. The percentage incidence of 77 in the cases of pulmonary tuberculosis is in accord with the observation of other observers, although Gerhardt believes that the true percentage is 90, and Rose 86. It is

usually estimated that about 10 per cent of all fatal cases of pulmonary tuberculosis have had a spontaneous pneumothorax at some time during the course, and that the complication develops in about 2 per cent of all cases. In tuberculosis it develops much more frequently in the cases that have softening than in those with a fibrous indurative type of disease. Pneumonia is a relatively more frequent cause in childhood. About 40 per cent of the total cases in children are of tuberculosis origin according to West<sup>3</sup>, but Stoloff<sup>4</sup> points out that in 35 per cent of the cases a non-tuberculosis pneumonia is the cause. All clinicians of extensive experience have seen pneumothorax develop as a result of empyema rupturing into the pulmonary tissue, inducing thereby a pyoneumothorax.

In generalized emphysema, pneumothorax rarely occurs, Saussier<sup>5</sup> reporting its occurrence five times in 131 cases. Stahlein<sup>6</sup> thinks that it does not cause more than 1 per cent of the total. Its development in generalized emphysema is rare, but of serious prognostic importance, because of the existent disease in the lungs and its subsequent deteriorating effect upon the heart. Kahn<sup>7</sup>, and Emerson and Beeler<sup>8</sup> have reported its occurrence in chronic asthmatics.

In my discussion I wish to emphasize particularly the so-called "idiopathic spontaneous pneumothorax," which evidently occurs relatively frequently, as the reports in the literature would indicate. In these no definite etiological agent can be uncovered from the history or the examination. These instances arise suddenly, as a rule, with or without dramatic symptoms in the

way of pain or local chest discomfort, and with a varying degree of shortness of breath. They tend to run a favorable course, going on to spontaneous recovery in a few weeks, with re-expansion of the affected lung and no vestigial objective effects. They are distinct from the other types in that they are rarely accompanied by effusion and exhibit no marked constitutional symptoms. This aids greatly in differentiating them from the far more serious tuberculous type. The good prognosis and the rarity of opportunities for necropsies have made it difficult to establish the pathological factors which may induce the condition. Because these cases are clinically so unlike the usual tuberculous cases, with the latter's tendency to exudation, constitutional symptoms and serious prognosis, many writers, particularly LeWald<sup>9</sup>, have sought to establish this condition as a definite specific clinical entity distinct from tuberculous causation. At the time of Dr. LeWald's presentation, a discussion by Drs. Miller, Willy Meyer and Lemon expressed the belief that they were probably always primarily tuberculous. Many isolated pathological postmortem findings tend to support this belief in a large measure. Two such patients with idiopathic spontaneous pneumothorax were examined with a thoracoscope at a meeting of the Swedish tuberculosis physicians, and in 1 a crater-like ulcer was found on the lung and in another a contracted scar, presumptively tuberculous. Kleeman<sup>10</sup> reported 2 cases that revealed tuberculosis, 4 and 7 years later respectively, and Haves reports a similar instance. LeTulle reports a case of spontaneous rupture with a single tuberculous nod-

ule, and West and Flint report a similar rupture of minute tuberculous foci. These instances are truly tuberculous. A pneumothorax originating at the site of a Ghon's primary node probably is an extreme rarity.

Of great interest has been Orth's<sup>11</sup> finding of a ruptured localized emphysematous bleb in an apex of the lung at postmortem examination. Fischer<sup>12</sup> reports three such cases, and Schoenfeldt one. In Pitts<sup>13</sup> case a ruptured emphysematous bleb was found with a torn adhesion near it. Tearing of a pleural adhesion is probably rarely a cause of spontaneous pneumothorax per se. Instances have, however, been reported, notably by Cahn and Brunner<sup>14</sup>, in which the ruptured emphysematous bleb was in close proximity to a pleural adhesion. Mönckeberg actually found a bleb on the edge of an adhesion. It is quite evident, therefore, that many instances find their origin in the rupture of a localized emphysematous vesicle somewhere in the lung, probably more commonly in the apex than elsewhere. Insofar as these emphysematous blebs may be due to previous tuberculosis, presently inactive, we may consider the condition as "paratuberculous," but I do not believe that tuberculosis is the sole factor in the production of these emphysematous vesicles. Ljungdahl<sup>15</sup> reports 2 instances in which rupture occurred a short time after an acute pleurisy. Two of my cases likewise followed such an event, and I do not believe that acute pleurisy can be assumed as being necessarily tuberculous in the absence of any effusion. It may be rheumatic or of a non-specific type. The most exhaustive study of the relationship between the



emphysematous blebs and spontaneous pneumothorax was made by Hayashi<sup>16</sup> in Fischer's laboratory, who in 1914 studied 77 cases. Three were due to a rupture of a localized emphysema in the apices, with evidence of a localized tuberculous fibrosis in the apex and pleural adhesions. He also found 4 other instances in which the bullae had not ruptured. They were found to empty with difficulty, but filled easily on inspiration, leading to gradual enlargement. This is in accord with the experimental work of Coryllos and Birnbaum<sup>17</sup> and the clinical observation of Jackson, Iucker and Lee<sup>18</sup>, that incomplete obstruction tends to lead to the development of emphysema. Hayashi points out that a primary apical induration as the result of a tuberculosis may induce a localized bulla and yet be entirely inactive otherwise from the standpoint of tuberculous activity.

I believe it may be assumed, therefore, that the idiopathic spontaneous pneumothoraces develop most commonly from emphysematous bullae, localized in character, their formation induced by fibrosis and induration in their proximity, and that these may be tuberculous or not. In the apex they undoubtedly are. The clinical course indicates that they are at variance with the usual tuberculous spontaneous pneumothorax, since they are much milder in character and are not due, as a rule, to the tuberculous process itself but rather the effects therefrom. Any pulmonary condition invading the pleuro-pulmonary surface may likewise be productive of this condition, though not as frequently. Tuberculosis is probably the most common, though only an indirect factor.

#### CASE I

*A Patient With Left Sided Total Pneumothorax of Eleven Years' Duration, Probably Tuberculous in Origin.*

J. Z., male, 41 years of age.

Family history negative to tuberculosis and no history of any contact with the disease. A physician in 1919 advised him that he had a dextrocardia while attending him for influenza. Attended again because of an acute respiratory infection in October, 1929, another physician advised him at that time also that he had a dextrocardia. After the latter illness an x-ray picture was taken and it was observed that the patient had a total pneumothorax of the left side with extreme displacement of the mediastinum and its contents to the right. The roentgenogram (Fig. 1) also showed an apparent old tuberculous process on the right side and a calcified pleural area on the side of the pneumothorax. The patient denies knowledge of any illness except as stated. The patient has been employed in moderately heavy manual labor.

On examination he has the general appearance of vigor. His heart is distinctly displaced to the right side and might be mistakenly assumed to be dextrocardia. The roentgenogram, however, indicates the true condition. Examination otherwise was negative except for the usual physical signs associated with a pneumothorax. The vital capacity was 1700.

*Comment:* This case is of interest because of the long duration of a pneumothorax, namely 11 years, with a strong presumptive evidence of its having been primarily tuberculosis, but never positively proved. The absence of effusion would indicate that no active tuberculosis process was present. The type of pneumothorax is either open or valvular. Bittendorf<sup>19</sup> reports a case of 25 years' duration as indicated by the history. Wieles<sup>20</sup> had an instance with a duration of 20 years. It would appear that ordinary manual labor is not inconsistent with a permanent total pneumothorax on one side.



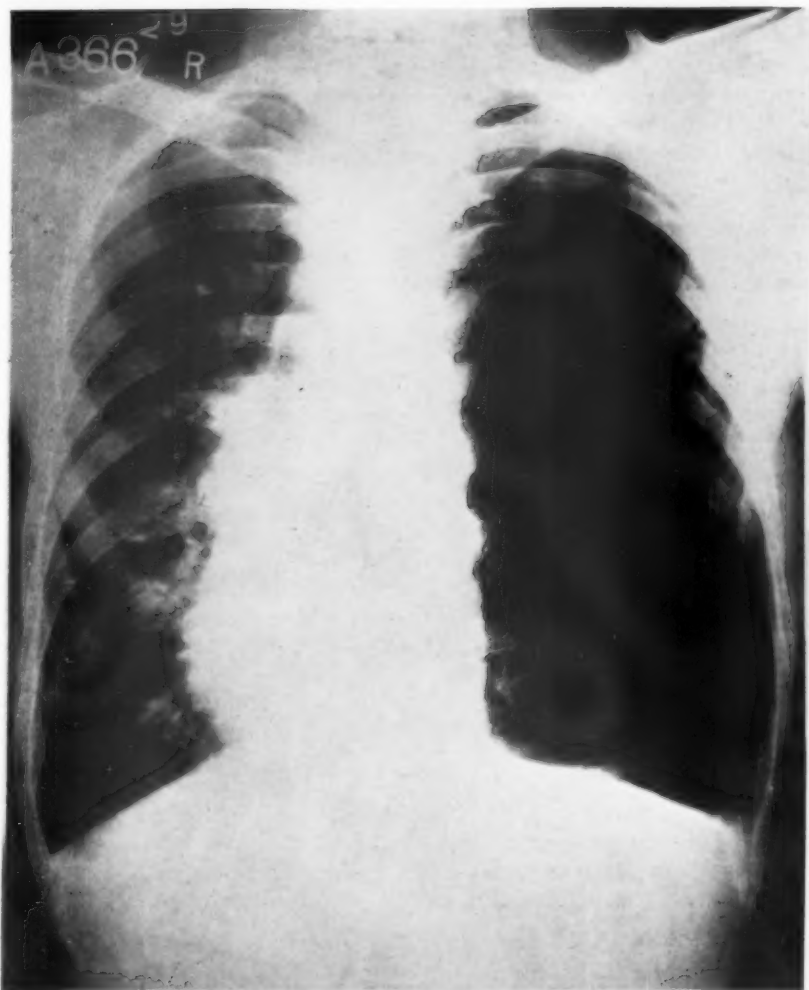


FIG. 1—Case 1: Spontaneous pneumothorax of eleven years duration with displacement of heart to right side—probably primarily tuberculosis.

## CASE II

*A Patient With a Bilateral Pneumothorax Due to a Contusion of the Chest Without External Evidence of Injury or Fracture of the Bones Comprising the Thoracic Skeletal Wall.*

G. J., male, 11 years of age, injured July 11, 1929, in an automobile accident, sustaining a simple fracture of the left thigh, with slight general bruising. There was considerable respiratory distress and cyanosis and the patient died 4 hours after the injury.

The x-ray picture (Fig. 2) revealed a pneumothorax on both sides, on the right side with a positive pressure, probably due to a valvular pneumothorax. Both lungs showed laceration of the lung tissue. Careful examination of the bones comprising the chest showed no evidence of any fracture, but an extreme compressibility of the thorax.

*Comment:* This is a case of bilateral pneumothorax due to an injury, without any external evidence or any fracture of the bones in the chest. It is of interest chiefly because of the difference in pressure in the two sides of the chest in spite of the bilateral nature of the condition, the right side showing a marked increase in positive pressure. This would indicate that there was no communication between the two pleural cavities through the mediastinum.

## CASE III

*A Case of Right Sided Partial Idiopathic Pneumothorax of a Recurrent Type, Peculiarly Associated With Menstruation and an Observation of 7 Recurrences in 21 Months.*

Mrs. R. H., first seen August 29, 1927, female, 38 years of age, married.

The family history negative except that the father had arthritis and iritis at one time.

Personal history: Always well except for the usual diseases of childhood, occasional tonsillitis, and an attack of acute pleurisy in 1925 without any complications and of one week's duration. Confinements uneventful.

At the time of her first examination, August 29, 1927, it was discovered that the

patient had a partial pneumothorax on the right side with a slight effusion in the right costo-diaphragmatic angle, and with a definite succussion wave on moving the patient.

In ten days the lung had expanded and the effusion had absorbed.

The patient was seen the day after the onset of her symptoms. She had slight pain in the right chest, which was coincident with the first day of her menstruation. It was observed later, during subsequent attacks, on January 10, 1928; August 8, 1928; September 29, 1928; March 4, 1929; April 5, 1929, and May 28, 1929, that the attacks always recurred on the right side and were exactly similar in the partial nature of the pneumothorax and the slight effusion in the right base, with healing and disappearance of the effusion in 10 to 14 days. These attacks were always associated with the menstrual period.

The patient is no longer under direct observation, but states that she still has attacks of a similar nature, but probably not quite so severe, since the last time she was observed in May, 1929.

*Comment:* There is nothing about this patient's history to indicate tuberculosis as more than a possibility. The history of an acute pleurisy may or may not be related to the symptoms ensuing 2 years later. The pleurisy may have been rheumatic in type in view of the paternal history and the patient's history of having had tonsillitis. The peculiarity of the recurrences lies in the association with the menstrual period. This association is difficult to explain, unless we may assume that there is aberrant ovarian tissue under the pleura which ruptures from time to time, leading to a partial pneumothorax and exudation.

## CASE IV

*Two Instances of Idiopathic Spontaneous Pneumothorax—One Total and the Other Partial—Without any Certain Evidence of Possible Etiology.*



FIG. 2—Case 2: Bilateral pneumothorax, following chest injury without fracture of bones comprising thoracic wall.

Positive pressure on right side with shifting of heart to left. Note pneumothorax on left, as well.

S. N., male, aged 24, single, first examined March 15, 1926, because of a pain in the left chest.

Examination revealed a friction rub in the left base.

The diagnosis of acute pleurisy was made.

The family history and personal history indicated nothing suggesting the possibility of tuberculosis, and the patient had always been in good health except for diseased tonsils.

On April 10, 1926, the patient returned with a history of having had a severe sharp pain in the left chest four days previous, unassociated with effort, and examination revealed a total pneumothorax on the left side. (Fig. 3.)

On May 21, 1926, all symptoms had disappeared, and the x-ray examination indicated a return to the normal without the development of any complications in the interim.

A few days later the patient returned with friction sounds throughout the left side of his chest, but no subjective symptoms except for a slight feeling of heaviness. A few days later these signs had disappeared.

#### CASE V

M. G., male, aged 32, single. Patient first seen at the office July 20, 1929, because of a sudden severe pain in the right chest, coming on without effort.

The family history indicated that one brother had died of tuberculous meningitis, but aside from this there was no history of tuberculosis in the family otherwise.

Personal history: The patient had had typhoid fever as a child, recurring attacks of tonsillitis, and a duodenal ulcer.

Examination: The physical examination on July 20, 1929, including the roentgenogram (Fig. 4) revealed a partial pneumothorax on the right side, and in the right base evidence of diaphragmatic pleural adhesions.

On August 12, 1929, all subjective and objective symptoms had disappeared, and the lung had re-expanded.

*Comment:* Aside from the fact that in Case V there was a history of tuberculous meningitis in the brother, there is nothing about the personal history of these patients or that of their family

otherwise which would indicate tuberculosis as a factor. The adhesions in the right base in Case V would indicate some old pleuritic disease. The rapid recovery, without complications, places these two cases into the group of idiopathic spontaneous pneumothorax. No positive etiology could be discovered.

#### CASE VI

*A Patient Whose Necropsy Revealed Localized Bullous Emphysema in the Right Apex Due to Fibrosis and Induration in Its Proximity. No Pleural Adhesions Were Present. No Evidence of Spontaneous Pneumothorax.*

J. S., male, 50, widower.

Family history: Wife died of tuberculosis in 1921, and one of his children also since that time of the same disease.

Personal history: The patient himself had an operation for a hypernephroma in April, 1923. Metastases had developed to the left antrum in 1929, and the patient entered the hospital in September, 1929, for relief from the malignant condition in the superior maxilla. The patient later died as the result of his metastasis and a terminal pneumonia. The autopsy incidentally revealed two small localized emphysematous bullae in the right apex (Fig. 5) in proximity to an area of fibrous induration, evidently primarily tuberculosis.

*Comment:* This case is illustrative of the fact that localized bullous emphysema occurs in the apex in association with disease in its proximity. These may occur without any clinical or roentgenographic evidence of disease. Rupture of such bullae when it does occur leads to pneumothorax, and might be considered clinically as idiopathic, and not related to tuberculosis, in the absence of pathological data.

#### CASE VII

*A Patient With a Very Large Bullous Emphysema in the Middle Lobe of the Right Lung, Evidently Developing to Enormous*

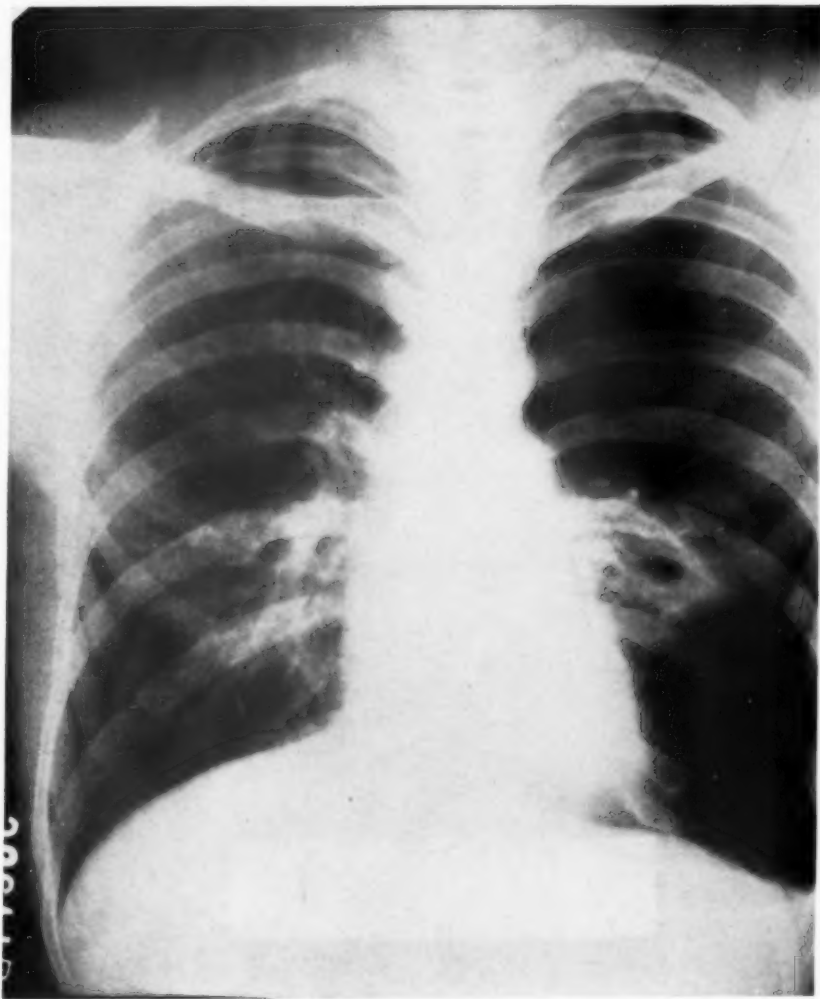


FIG. 3—Case 4: Complete pneumothorax on left side of idiopathic type.

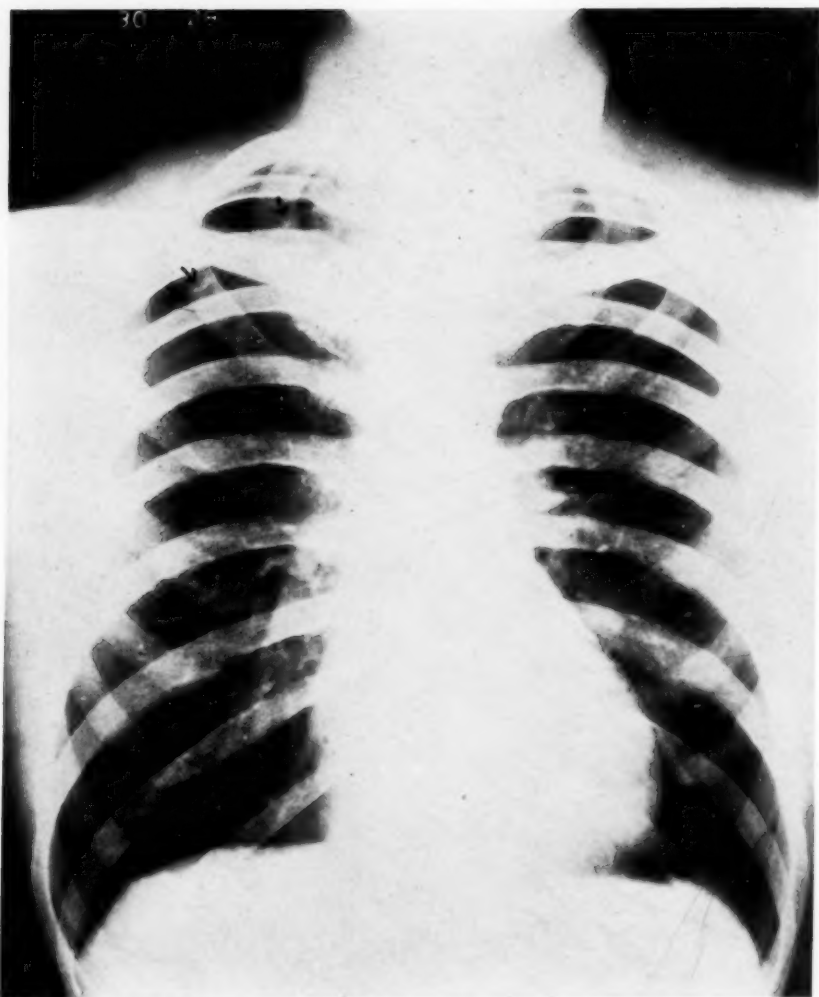


FIG. 4—Case 5: Partial pneumothorax on right side—idiopathic or primarily tuberculous. The only suggestion of tuberculosis was the history of tuberculous meningitis in a brother.





FIG. 5—Case 6: Photograph of the apex (only) of the right lung with several unruptured emphysematous blebs. These blebs when ruptured are probably the usual cause of idiopathic spontaneous pneumothorax.

*Proportions Within 30 Days, Death Ensuing Without the Development of a Pneumothorax.*

S. M., male, 46 years of age, first seen August 15, 1927, with classical symptoms of Graves' disease, and a metabolic rate of 50+

Prepared for operation with Lugol's solution, and thyroidectomy performed on September 3, 1927, when his condition was satisfactorily stabilized. He left the hospital September 14, 1927, after an excellent, uneventful recovery. A roentgenogram taken September 8, 1927, was negative.

On October 31, 1927, the patient returned, with a history of acute illness for three weeks prior to his admittance to the hospital. The patient had a diastolic and systolic murmur, scattered areas of bronchopneumonia, and a right pleural effusion. (Fig. 6.)

On November 2, 1927, a quart of clear fluid was removed from the right pleural cavity. The patient died the next day.

Necropsy revealed a bacterial endocarditis of the aortic and mitral valves, infarction of the spleen and kidneys. The lungs showed adhesions near the apex on both sides, and several large bullous emphysematous areas (Fig. 7) along the anterior surface of both lungs, one on the anterior portion of the right middle lobe the size of a foetal head. The pleural cavity on the right

side contained one quart of clear fluid. Bronchopneumonic patches were evident throughout both lungs.

*Comment:* This case would indicate that an enormous bullous emphysema may develop in a short period of time—in this case certainly within 1 month. Tuberculosis was not a factor in its production. Any pulmonary condition, acute or chronic, which does not permit of the emptying of a certain lung area, but does permit filling with air, leads to emphysema. This is in accord with the experimental work of Coryllos and Birnbaum<sup>17</sup>, (Fig. 8) who found that a valvular obstruction leads to emphysema in the parts tributary to the obstruction.

#### CASE VIII

*A Patient With a Massive Saccular Emphysema Filling the Right Chest Cavity, With Increased Intrascapular Pressure, But Without Rupture Into the Pleural Cavity.*

R. G., male, 21 months of age.

Family history negative. Father and mother living and well. No other children in the family.

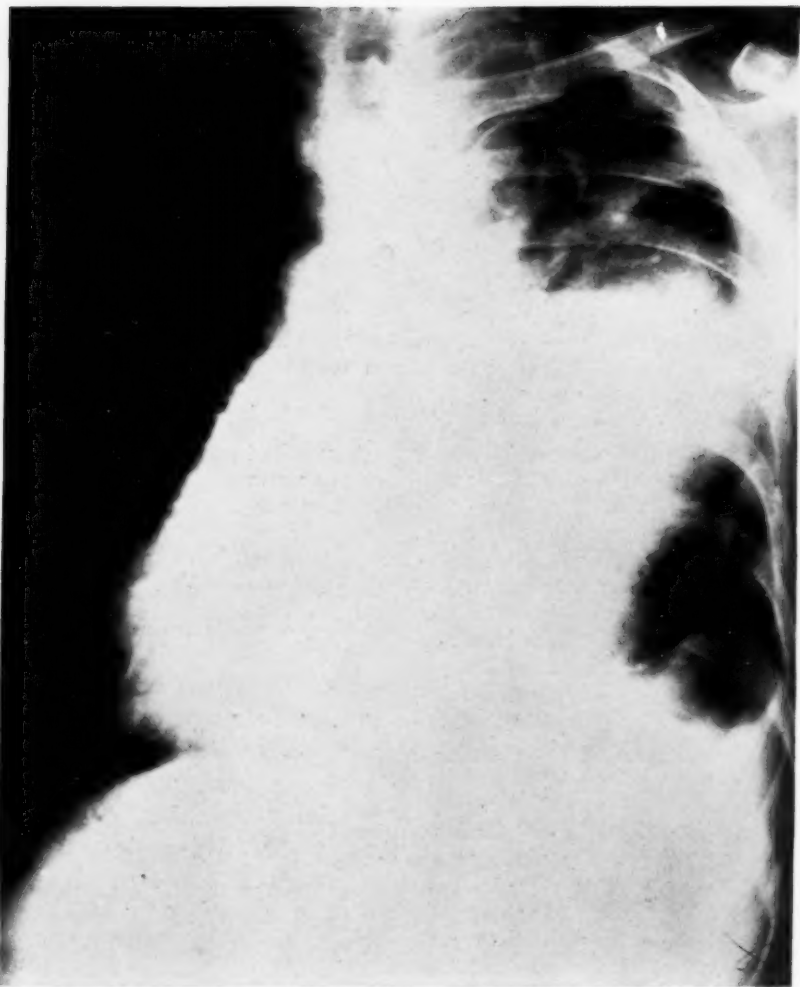


FIG. 6—Case 7: A large emphysematous bulla in the lower right lung field with pneumonic area above (Necropsy report).

Indicating rapid development in about one month's time without rupture and pneumothorax.



FIG. 7—Case 7: Photograph of right lung removed at necropsy of Case 7. Note large emphysematous bulla of recent development in lower half of photograph. This had not ruptured before death.

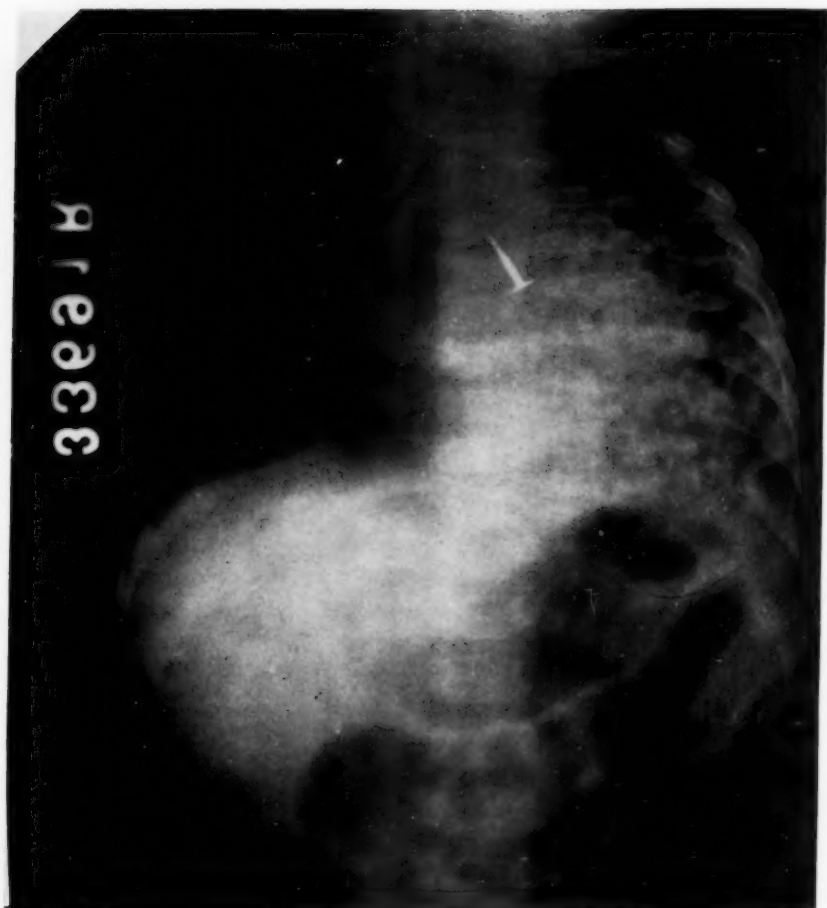


FIG. 8—Foreign body partially obstructing main left bronchus in a child, illustrating diffuse emphysema resulting therefrom. See text.

Past illnesses: Child was full term. Birth weight 7 lbs., 4 oz. Measles at 8 months, but never ill otherwise. Breast fed for 6 months.

First examined April 9, 1928. Gave a history of having been ill for 5 days with a slight fever, without a cold or cough, and in an improved and convalescent condition apparently, but with a history of having lost 7 ounces in the past week.

On examination it was observed that the breath sounds were entirely absent in the right lung, but present on the left, with an extreme hyperresonance on percussion. The hands and feet were a trifle cold, possibly from lack of circulatory vigor. X-ray picture taken of the chest (Fig. 9) indicated an enormous spontaneous pneumothorax with increased pressure. The Von Pirquet and Mantoux were negative. Blood counts normal, white blood count 14,000, differential normal.

Since that time the patient has been under observation, without any material change in the condition. In May an attempt was made to reduce the positive pressure by the introduction of a needle, but because of the onset of discomfort in breathing and a cough the effort was discontinued after about 300 cubic inches of air were removed. An x-ray picture taken immediately thereafter showed the outline of a large emphysematous shell in the right chest (Fig. 10). Subsequent consultation elsewhere led to a diagnosis of lung cyst, but I believe that the diagnosis of a saccular emphysema is more in accord with the objective findings. Within the past few months several efforts have been made at reducing the intrasaccular tension by the introduction of a needle, and at one time a response was effected with a partial inflation of the lung so that it was visible to the right of the spine in the roentgenogram. The intrathoracic pressure, however, increased, and the lung shadow to the right was again effaced with the displacement of the mediastinal contents to the opposite side. The child's condition at the present time is unchanged.

*Comment:* This child evidently has a large massive saccular emphysema of the right lung, with a marked increase in the intrasaccular pressure, resulting

in a collapse of the remaining tissue of the right lung, so that it is quite invisible on the roentgenogram. The manner of origin of this emphysematous sac is difficult to understand as the history does not supply any data on this point.

#### SUMMARY

1. Spontaneous pneumothorax is any pneumothorax which develops aside from external causes. Idiopathic spontaneous pneumothorax is that rather frequent type in which clinically no cause is demonstrable. Idiopathic spontaneous pneumothorax has a favorable course, unattended by serious symptoms or complications, as a rule, and tends to heal in a few weeks, with no residual findings.

2. The cause of idiopathic spontaneous pneumothorax from a necrotic standpoint is difficult to establish because of the rarity of necropsy findings, but it would appear that localized emphysematous blebs are the most frequent cause.

3. These localized emphysematous blebs may be the result of indurative processes in the subpleural pulmonary tissue, regardless of primary origin; or of emphysematous processes in the proximity of adhesions. It is doubtful if pleural adhesions are, per se, a frequent cause.

4. Tuberculosis is probably the most frequent primary cause. Any condition leading to the formation of emphysematous bullae may be likewise a factor.

5. Instances of idiopathic spontaneous pneumothorax are cited, and certain instances of saccular emphysemata of varying size, unassociated with pneumothorax, reported.

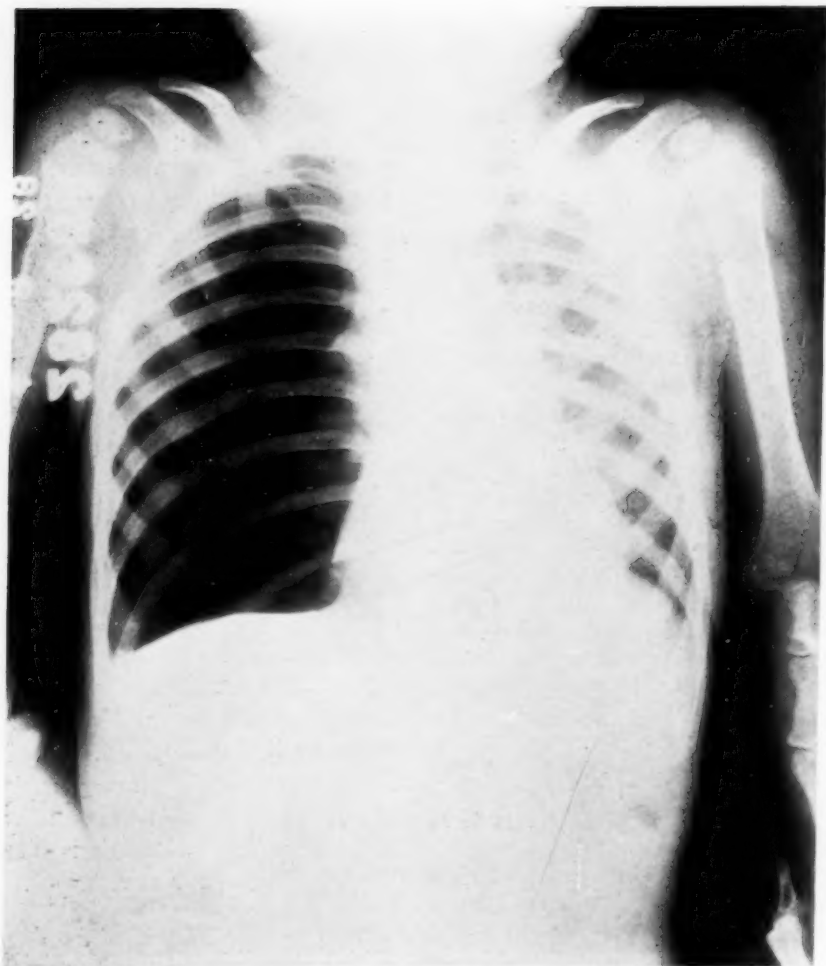


FIG. 9—Case 8: An infant whose roentgenogram shows what appears to be a spontaneous pneumothorax, congenital or acquired—probably a huge bulla. See Fig. 10.





FIG. 10—Case 8: After attempt at aspiration because of extreme positive pressure in right pleural cavity.

Note delineating saccular outline in right pleural cavity, suggesting a huge pleural sac of emphysematous type.

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## General Management of Pulmonary Tuberculosis\*

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THE presentation of a paper on such a subject to this group would be like "carrying coals to Newcastle" were it not for the wide difference of opinion among sanatorium physicians regarding the use of rest which, of course, forms the backbone of the sanatorium treatment of tuberculosis. We glibly tell the patient that sanatorium treatment offers him his best chance for recovery. But what do we mean by sanatorium treatment and does it mean the same thing to all physicians? Nearly all physicians agree that it means bed rest during the acute febrile stages but there is not the same unanimity of opinion regarding the use of rest after the acute phase has passed and the long period of convalescence has begun. Some believe that merely keeping the physical activity below the fatigue level is all that is necessary during this period. Others believe that bed rest should be continued long past the period when the pulse and temperature have become normal, even possibly until fibrosis has ceased. Such a wide difference of opinion concerning the use of rest indicates that an analysis of the

basic principles underlying its use is warranted.

What rest means to the various physicians depends upon what each physician expects to accomplish through its use. This in turn depends upon the extent to which he believes that rest can influence the mechanism of recovery, as it is revealed in Koch's phenomenon. Von Pirquet called this phenomenon allergy, indicating broadly a condition of altered reactivity. As he used the term allergy included both the acute inflammatory and the immunological phases of this altered reaction. The exact relationship of these phases to each other and their significance in tuberculosis are not yet determined. Without attempting to settle the controversy, this discussion will consider them as separate yet related and co-existing apparently antagonistic reactions. Allergy is now limited to the acute inflammatory phase of the altered reaction which, because of the acuteness of the response, is a source of danger to the host. This phase of the reaction is due to tissue hypersensitivity and accounts for much of the symptomatology of tuberculosis. Immunity is now limited to that increase in resistance which tends to protect the host against tuberculosis by retarding the growth and limiting the spread of

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tubercle bacilli. Just how this is accomplished is not known but it is represented in part at least by an increase in the ability of the body to form fibrosis which prevents the circulatory exchange between the tubercle and the body. This phase of the reaction is responsible for whatever tolerance the body may develop towards tuberculosis.

From innumerable experimental studies, Krause has concluded that tuberculosis represents a general infection rather than a local one with a rather frequent moving about of bacilli, resulting in a few visible foci, may be only one, and several concealed ones, all more or less held in check by the relative immunity which develops as a result of the first infection. He believes that this gives us a picture of tuberculous infection somewhat similar to that of syphilis with its microorganisms rather widely distributed before its focus of inoculation comes to light.

Tuberculous infection, however, causes no symptoms until allergy develops. Then the symptoms vary from those of slight moment to those of great severity depending upon the degree of allergy present and the resistance of the body, as both are modified by the number and virulence of the bacilli and the frequency of implantation. If the allergic reaction is so intense as to overcome the immunological reaction, fatal tuberculosis may result. If, on the other hand, the resistance or immunity is greater than the inflammatory reaction, the symptoms subside, healing begins and may continue even until cavities disappear. Both of these processes, that is, acute progressive tuberculosis and healing or fibrosis may be very closely followed on x-ray

plates. Because the immunity which develops is only relative and never complete, there is always the danger that healing will not be firm and sound before a new focalization occurs and the process begins over again.

Fortunately for most of us, the infection of tuberculosis is usually moderate, calling forth a rather slight allergic reaction with mild general symptoms and with a rather high degree of relative immunity and with a long enough time between periods of focalization for that immunity to become so well established that clinical disease does not develop. Sometimes, however, something happens such as acute illness, over-fatigue, massive infection, or the unusual "stresses of environment" to upset the delicate balance between allergy and immunity and allergy again arises and all of the previously, partially healed lesions become active again and clinical tuberculosis ensues.

There are certain factors in bodily growth which should also be discussed in the consideration of any outline for the general management of tuberculosis. The first is the marked atrophic changes which take place in the lymphatic system shortly after the advent of puberty and which continue throughout life. The second factor is that the ability of the body to form fibrosis increases from birth until old age. One cannot but wonder whether these growth factors influence, through a modification of allergy and immunity, the type of tuberculosis which develops before and after puberty. Theoretically both immunity and allergy should be greater in childhood than in later life because of the recentness of infection.

Therefore, the bacilli should be fixed where they lodge, i.e. in the tissues, more promptly and the acute manifestations of tuberculosis should be more marked in childhood than in adult life. But childhood tuberculosis is essentially a lymphatic disease rather than a tissue disease and is usually benign but with tremendous possibilities for future damage. Adult tuberculosis on the other hand is essentially a tissue disease and constitutes most of our clinical tuberculosis. If these growth factors do influence, to some extent at least, the type of tuberculosis which develops before and after puberty, then the mode of living required to control tuberculosis might be modified according to age. The child requires much less strict supervision as regards rest than does the young adult.

No reason need be given this group why the lungs are involved in the tuberculosis process more frequently than any other organ of the body. Attention, however, should be called to the fact that tuberculosis can develop in any other organ of the body. When it does, it is usually the result of a metastatic infection from a pulmonary focus. Because of this, the general management of tuberculosis should include a thorough search for foci in any organ of the body and a plan of treatment that will include both the local and general conditions.

All of these factors of allergy and immunity, of infection, of growth and of metastasis enter into our picture of chronic fibroid tuberculosis. In its changing allergic state and in the variations in resistance are to be found the explanation of the relapses and remissions so common in chronic tuberculo-

sis. It is for this type of disease and based upon these phenomena that we are attempting to outline a new mode of living.

The foundation for this new mode of living is rest which alone of all of the cures advocated for tuberculosis has stood the test of time. In the past rest was used in the treatment of tuberculosis as it was in other diseases, that is, only while there were symptoms of toxemia or for a short time after the symptoms had disappeared. Then it was discontinued and supervised exercise so regulated as to keep the patient's physical activities below the fatigue level was begun. Relapses occurring under this treatment which was adequate for the other diseases, were considered unavoidable, due to the nature of the disease, or "to the will of Allah." When we began to take serial x-ray plates we were better able to correlate our cases clinically with what was discovered at the autopsy table. Thus we learned that subsidence of symptoms meant not a cure as it did in the other diseases but merely that the acute inflammatory process, which is due to the circulatory exchange between the body and the tubercle, was quieting down and that the cure as represented by fibrosis or encapsulation, upon which the prevention of this circulatory exchange depends, was just beginning. Further study gave visible proof of two facts, first, that the formation of fibrosis was enhanced by rest and retarded by exercise just as the union of broken bones is enhanced by rest and retarded by constant motion, second, that relapses due to pulmonary strain were much more likely to occur while fibrosis was forming than after encap-

sulation had become complete. This indicated that our former failures might not be due "to the will of Allah" but to treatment which permitted increased pulmonary strain before the healing was strong enough to stand it. The resulting conclusion was that if bed rest, which reduces pulmonary movement to a minimum consistent with living, and, which had brought about a subsidence of symptoms and the beginning of the immunological response had been continued until that response had ceased, encapsulation might have been more complete and relapses less frequent.

In preparing the following standards for the use of rest in the treatment of tuberculosis our sole motivating idea has been the restoration of the patient to the status of a wage earner in the shortest possible time consistent with a fair degree of certainty that his recovery will be as permanent as possible, thus reducing the frequency of relapses. We believe that this result can be best secured by one long term admission rather than by several short term admissions.

There are four questions which should be considered in any plan governing the use of bed rest in the treatment of pulmonary tuberculosis. First, what patients need bed rest? Second, how intensive should bed rest be? Third, how long should bed rest be continued? Fourth, how can the patient's morals be conserved during a period of prolonged bed rest?

*First.* As we believe that better results will be obtained in all cases, that is, the non-toxic as well as the toxic, if pulmonary activity is reduced to a minimum, every patient admitted to the

Sanatorium is put on bed rest, which means that he must remain in bed twenty-four hours a day. The only exceptions to this rule are certain "repeaters" and elderly people and old chronic fibroid cases where the problem is more of a public health than a medical one, and certain cases of doubtful diagnosis where all of the evidence at hand points to a non-tuberculous condition or a case of non-clinical tuberculosis. The reason for the use of bed rest during the period of toxemia and possibly for a short time afterwards is apparent to all. The advisability of the use of rest for the non-toxic patient is not so universally accepted. However, as the recovery for the non-toxic patient as well as for the toxic patient depends upon how complete the fibrosis is and as fibrosis forms more rapidly and more completely under conditions of rest than it does under conditions of even modified exercise, it follows that the atoxic patient needs bed rest and is greatly benefited thereby. Also, absence of symptoms and a sense of apparent well-being causes the average atoxic patient to minimize the significance of his trouble. This often results in a false sense of security which must be counteracted if he is to recover his health and retain it. Such a state of mind is a veritable sword of Damocles and must be coped with as such. Bed rest by impressing the non-toxic patient with the seriousness of his disease and with the necessity for careful treatment does much to enable him to handle his problem.

*Second.* The intensiveness of the bed rest varies with the age of the patient—the character of the lesion—



the symptoms, and the progress of the patient as it is revealed in serial x-ray plates at intervals of two to three months. In general the teen age group and young adults need much more intensive rest than does the child or older adult. A "sloppy" caseous lesion needs much more intensive rest than does a chronic fibroid lesion. Bed rest need not be so intensive after the symptoms of toxemia have disappeared, the patient's general condition has returned to normal and the lesion is progressing satisfactorily from an x-ray point of view.

Because of these variables we have attempted to provide certain standards governing the type of case and condition of the patient in each group.

In doing so we realize fully that such rigid standards will be unbearable for some and concessions will have to be made. Obviously it is better for such people to read, to sit up in bed or even to go to the bathroom than to lie fighting restraint like a caged animal. What we have tried to do is to establish an ideal with the understanding that it may have to be modified at times.

TABLE I  
CLASSIFICATION OF BED REST  
*Glen Lake Sanatorium*

ACTIVITIES	INTENSIVE (1)	STRICT (2)	REGULAR (3)
Sit up in bed for meals and other purposes	No	No	Yes
Meals	May or may not feed himself lying on side after food has been cut	Feed himself lying on side	Feed himself sitting up
To x-ray, lamp or treatment room	Only in the bed	Only in the bed or on a litter	In wheel chair
Occupational therapy, reading, writing, etc.	No O.T. work No writing Certain cases may read if bookrest is used	Yes, while on side or lying down	Yes, sitting up in bed
Type of disease	Toxic—febrile Caseous non-febrile Certain far advanced cavity cases that are non-operable receive prolonged intense bed rest	Non-toxic fibro-caseous lesion. More extensive fibroid lesion. Patients in group (1) who have improved sufficiently to stand more freedom in bed	Non-toxic fibroid lesion. Long standing lesion of any degree group (1) and (2) because of sufficient improvement

It is impossible to state definitely just how long a patient is held at each step. Dependent upon the factors mentioned above, i.e. the age, the extent and character of the lesion, the symptomatology and what is happening to the lesion as determined by x-ray pictures repeated every few months, the patient is either held in a position of status quo or is advanced to the next step.

We have divided bed rest into three groups (1) intensive bed rest, (2) strict bed rest, and (3) regular bed rest.

(1) *Intensive bed rest.* The patient spends the entire twenty-four hours as quietly as possible. He is not allowed to read, write or to sit up in bed but may or may not feed himself after the food has been cut up. The acute febrile case and the young adult belong in this group.

(2) *Strict bed rest.* About the only difference between this group and the former is that a limited amount of reading and writing and occupational therapy work may be done. In general, the patients in this group are those with a non-toxic fibro-caseous lesion or more extensive fibroid lesion or those patients in Group 1 who have improved sufficiently to warrant a slight amount of mental activity.

(3) *Regular bed rest.* This is the type of bed rest used by the atoxic patient who is waiting for his fibrosis to cease forming. These patients feel good—they may sit up in bed, read, write and do occupational therapy work or vocational training but they are always cautioned to remember that mental activity is exercise and therefore, that it should always be kept below the fatigue level.

We believe further that the desired results will be secured more rapidly if bed rest is reinforced with postural rest or when this is not advisable, the use of shot bags, as described by Webb, Forster and others.

The third question is, how long should bed rest be continued? We believe that the patient should be kept in bed twenty-four hours a day until the

result expected from bed rest has been obtained. That involves, of course, the question, what is the desired result? Is it merely a subsidence of symptoms and a quiescence of the disease or as complete an investment of the tuberculous process as the immunological response can produce? If the latter condition is the desired one, then no change should be made in the treatment as long as fibrosis is going on. The standard which the surgeon applies in the treatment of bone and joint tuberculosis, namely, fixation until ankylosis and healing ceases, applies just as aptly in tuberculosis of the lungs and should be used in pulmonary disease. Furthermore, there is general agreement that pneumothorax which produces a much more complete rest of the diseased lung than does bed rest, should be carried out for at least three or four years. If such rigid standards are necessary where complete rest of the diseased part can be obtained, then certainly just as rigid standards are necessary when relative rest or bed rest is used. In view of that, how can any one recommend that rest be discontinued and exercise commenced after the pulse and temperature have been normal for only a few weeks. Certainly the length of time over which localized rest is deemed necessary is one of the best arguments for prolonged bed rest. Under this standard, of no change in the treatment while fibrosis is going on as seen in x-ray plates, the duration of bed rest will vary for each individual patient, the early cases needing a much shorter period of bed rest than does the advanced case. It is interesting to note how frequently no improvement in the lesion can be detected by means of

stereoscopic x-ray plates until the symptoms of toxemia have disappeared and the body has made good its deficit. Our experience in this has borne out Stewart's conclusion that if six months rest in bed has had some effect on the frame and figure and symptomatology of the patient, maybe another six months in bed will have the like effect upon the tuberculous lesion.

Admittedly there are cases which will improve and even heal enough for resumption of ordinary life without such rigid treatment. As yet we have no test *but the trial and error method* for determining the unusual resistance which such individuals must possess and hence no index but that for making an exception of these cases. If that method is tried and the case proves to be one of *only* usual resistance, the results may be exceedingly disastrous. So the safest plan is to use bed rest even longer than absolutely necessary for in the words of Trudeau, "I know I have hurt nobody by rest but I am quite sure I often have by allowing them to exercise." Pratt in advising prolonged bed rest writes in 1918, "It takes a long time for scar tissue to form, hence according to the extent and the severity of the disease months and years must elapse after the development of a fresh tuberculous process before pulmonary exercise can be undertaken without danger.

V. B. #3924—Min. (a). Single.

Admission—Temperature range first three weeks—97 to 99.6° (rectal).

Pulse range first three weeks—68 to 92 with two jumps to 106 and 108.

Weight 137¼.

Sputum examination negative but guinea pig inoculated with specimen of sputum developed tuberculosis.

8-19-29—Entrance x-ray. Fibroid p.c. lesion 2nd I.S.L. and thickening of right interlobar pleura.

Two subsequent x-rays showed clearing.

Next x-ray 7 months after admission shows no change so patient allowed to go to bathroom.

8 months after admission patient is still going to the bathroom.

Weight 145#.

G. S. #3384—Male, White, M.A. (b). Single.

Admission—Temperature range first twelve days was 98 to 99.4° (rectal).

Pulse range—68 to 86.

Weight 135#.

Sputum—Gaffky IV.

Previous history—Well until June, 1927, when he had the "flu" from which he did not seem to recover. By August he had developed a dry cough and had lost 10 pounds. His physician told him he was anemic. His condition did not improve and in September his physician told him that he had inactive tuberculosis.

In February, 1928, he developed pleurisy with fever and in the latter part of March a consultant diagnosed tuberculosis and he was sent to the Sanatorium.

Entrance examination—+ on right. Left negative, checked by three consultants.

Entrance x-ray—Dense fibroid p.c. infiltration right apex.

Hazy p.c. infiltration in left to 2nd and 3rd I.S.

After fifth month sputum became negative and has been negative since. Weight 175#.

Subsequent x-ray shows continuous improvement until that one taken 13 months after admission. This shows no improvement so patient is allowed to go to the bathroom.

Next x-ray shows improvement so patient remains in status quo.

19 months after admission x-ray shows apparently stationary lesion, so patient started to meals.

Exercise begun—20½ months after admission.

22 months—x-ray—no change—exercise increased.

These two cases illustrate the difference in the length of time bed rest may be used in a minimal case and a moderately advanced case. Both show excellent symptomatic and anatomic results, as shown by clearing and fibrosis as seen on the x-ray plates.

The fourth question is, what will happen to the patient's morale during such a period of prolonged bed rest? We admit that such a period of prolonged bed rest may possibly weaken the morale of the patient so that he becomes hospitalized. Therefore, when the progress is satisfactory, we believe that mental exercise should be gradually increased while the patient is still observing physical rest. This may even include a course of vocational rehabilitation, instructive reading and occupational therapy carried out under medical supervision. This will keep his mind active so that he is better able, upon his discharge, to adjust himself to the new environment of the working world than he would have been otherwise. In planning this, one should never forget that mental exercise is exercise and may be as injurious as physical exertion. Therefore, this plan of educational development should be carried on under medical supervision.

Some will claim that bed rest over such a long period of time will cause gastro-intestinal disturbances and degeneration of the muscular system. The gastro-intestinal disturbances can be controlled by diet. As for the degeneration of the muscular system, what of it? What are we treating, the muscular system or diseased lungs? If we are treating a diseased lung, then when the lungs are well the muscle tone can easily be restored by proper exercise.

After healing has ceased under the use of bed rest and the process has become stationary, as determined by x-ray pictures, another type of treatment is necessary. What this is will depend upon the extent of the healing. If slight, then dependent upon the type of lesion, i.e. old chronic fibroid, fibro-caseous or caseous, exercise or collapse therapy is indicated. If marked, and nearly complete, then exercise so carefully regulated as to promote further healing rather than to interfere with it is indicated. This can best be accomplished by using the same standard for increasing exercise as was used in determining when bed rest should be discontinued and exercise begun. That is, "while the patient is improving no change in the treatment is indicated." So, if fibrosis, which has become stationary under rest begins again under a certain amount of exercise, say, on going to the bathroom or to the dining room or on one-half hour or more exercise, then this amount of exercise should be continued until fibrosis or favorable pathological activity ceases. When it does, of course, exercise should be increased again. Under this program fibrosis may continue until there is practically no lesion remaining. It is obvious that this stage in the treatment of tuberculosis is a very critical one. Any over-exertion or indiscretion on the part of the patient may upset the delicate balance between allergy and immunity and result in a spread of the disease and a new outbreak of clinical tuberculosis thus forcing the patient to start his "cure" all over again. Therefore, the physical activity should be kept within the limits which will permit

the continuation of fibrosis. Guiding a patient through such a period requires an understanding of tuberculosis infection, the pathological response of the body to its presence and the resulting symptomatology, both local and systemic. The chief systemic symptoms are those represented by chronic fatigue, unstable temperature and pulse and indefinite gastro-intestinal disturbances.

Because of certain factors of growth previously mentioned, the limitation of the activities of the teen age and young adult group should be greater than for any other age of life.

Nothing has been said so far about the question of food and fresh air in the treatment of tuberculosis. We believe that a diet adequate in calories, vitamins and minerals for the man in health is suitable for the consumptive. In the past, the value of fresh air has been over-emphasized. The body can receive all the stimulation it needs in a well ventilated room, so constructed that it is not too warm in summer and with enough radiation in winter to keep the day temperature at about 65° and the night temperature about 40°.

### CONCLUSIONS

In outlining the general management of pulmonary tuberculosis one should consider all of the factors; infection, allergy and immunity, growth and metastasis and should so plan the treatment that the acute inflammatory symptoms can be controlled and that the formation of fibrosis will not be interfered with but will be enhanced. This can best be accomplished by adhering to the maxim that as long as fibrosis is forming no change in the treatment is necessary. If the improvement under rest has been marked, then exercise carefully controlled is necessary. If on the other hand, the disease shows little or no improvement after a few months rest in bed then, dependent upon the type and condition of the lesion, either exercise or some form of collapse therapy is indicated.

Note: Under the plan of general management as outlined above, 33.9 per cent of our pulmonary cases now in residence have had or are now receiving some type of collapse therapy.

The results obtained under this plan in 1929 as compared with those of 1925 when we began to follow this outline are very interesting.

### CONDITION ON DISCHARGE

	Improved or Better Than Improved		Unimproved or Dead	
	1925	1929	1925	1929
Far-advanced .....	20%	42.5%	80%	57.5%
Moderately advanced ....	63%	83.2%	37%	16.8%
Minimal .....	86%	89 %	14%	11 %
Extra-pulmonary .....	85%	94.8%	15%	5.2%
Childhood .....	95%	95.8%	5%	4.2%

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## Myxedema Heart With Report of One Case

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**M**YXEDEMA heart is now a recognized clinical entity. In the last few years cases have been reported from various parts of the world. I have been able to collect 21 authentic cases from the literature with teleröntgenograms and electrocardiograms revealing the condition of the heart before and after thyroid therapy.

The slides shown here are from a previously unreported case now on the medical service at the Minneapolis General Hospital. I am greatly indebted to Dr. G. Fahr, Chief of the Medical Service, for the privilege of reporting this case. The patient is a female, 48 years of age, with a history of myxedema of over eight years duration.

On admittance to the hospital six months ago, June 21, 1929, because of frequent, burning urination due to a urethritis, she presented a typical myxedema. She had the broad expressionless face of myxedema, the skin was a sallow color, thickened, in folds, dry and scaling. The scalp was dry and in places the hair was thinned out. She had a disinterested stare. There was marked mental retardation and slow muscular movements. She was deaf and her memory was very poor. She gave a history of dyspnea on exertion for the past five years. Cyanosis of the lips was present and on examina-

tion there was found marked generalized cardiac enlargement, a systolic murmur at the apex, a liver palpable one finger below the costal margin in the midclavicular line, râles in the lung bases and a pitting edema over the lower extremities and sacrum. The temperature, pulse and respirations were normal. Blood pressure was 115/60. Basal metabolic rate was  $-27\%$ .

At this time the blood was normal. The urine showed a faint trace of albumin, occasional red cells, a few pus cells. Free hydrochloric acid was absent from the stomach after histamine.

At this time a six foot heart plate revealed a transverse diameter of 19 cm. The enlargement seemed to involve all chambers of the heart. The electrocardiogram showed very low T waves, PR 0.2. She received 24 cc. of Tincture Digitalis (1 cc. =  $1\frac{1}{4}$  cat units) in the next 14 days without change in the size of the heart. Digitalis was now stopped and she received 50 grains of Armour's thyroid extract in 17 days with a resultant decrease in size of the heart to 13.9 cm. which means a reduction of 5 cm. in the transverse diameter. The electrocardiogram returned to normal. The change in the patient was remarkable, she lost 21 pounds in weight, became active mentally and

physically and took great pride in helping with the ward work. The cyanosis, dyspnea, palpable liver, râles in the lung bases, and pitting edema had all disappeared. Her vital capacity rose from 1700 to 2200. At the end of 7 weeks she had received 175 grains of thyroid and the transverse diameter of the heart was 12.8 cm. The electrocardiogram was normal. Basal metabolic rate +15%. Thyroid was now stopped. The heart began to dilate and in 4 months had dilated to a transverse diameter of 17 cm. The electrocardiogram showed a return to the abnormal findings present on admission, namely iso-electric T waves, PR interval of 0.2. All this time the patient was kept

doing approximately the same amount of work. All her former symptoms and signs of cardiac decompensation began to return, the basal rate dropped to -32%. Under the fluoroscope scarcely any movement of the cardiac borders could be seen. All of her former symptoms of myxedema returned; she became very sluggish, mentally and physically, and gained six pounds in weight. She no longer wanted to help around the wards and complaining of the cold was given a bed in one corner of the ward where she could keep all windows closed. Thyroid medication was resumed on February 11, 1930, and we do not have the slightest doubt but that in a few weeks she will be bright and

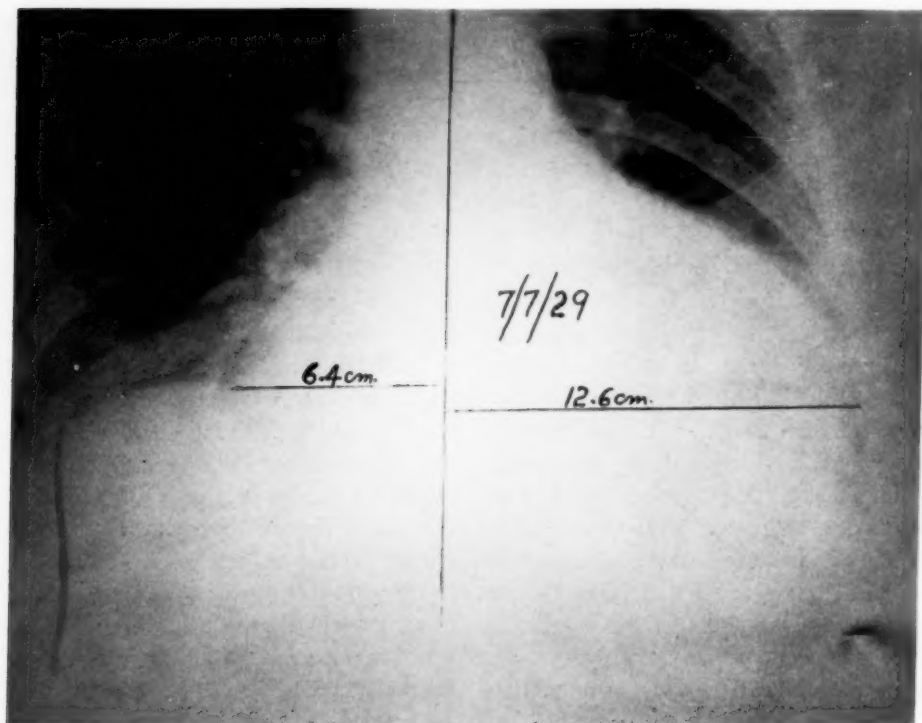


FIG. 1. Six foot plate taken 7/7/29 before administration of thyroid.

cheerful with a normal sized heart and a disappearance of all the present signs of cardiac decompensation.

Myxedema heart was first described by Zondek<sup>1</sup> in 1918 when he reported four cases from Krause's clinic in Berlin. At that time he described: Generalized heart enlargement, normal blood pressure, slow pulse rate and electrocardiographic changes. Under the fluoroscope the heart appeared very sluggish in its movements. He noted low or absent P waves, absent T waves and changes in the QRS complexes. On thyroid his heart underwent changes similar to the present case. The first cases reported in this country were those of Dr. G. Fahr<sup>2,3</sup> in 1925 and 1927. He not only reduced the hearts

to normal size, but caused them to dilate again on withdrawal of thyroid.

All of the cases of myxedema heart seen in Dr. Fahr's clinic have had P waves on the electrocardiogram. Most of his cases have had negative T waves in one or more leads, abnormal QRS complexes and abnormal PR intervals, all of which have returned to normal on thyroid medication. Three of his cases had a negative QRS in lead 3 which returned to normal on thyroid. The present case developed a negative QRS in lead 3 on thyroid and returned to normal when the heart dilated due to withdrawal of the thyroid extract.

There have been cases reported of enlarged hearts in myxedema that do not decrease in size on thyroid, al-

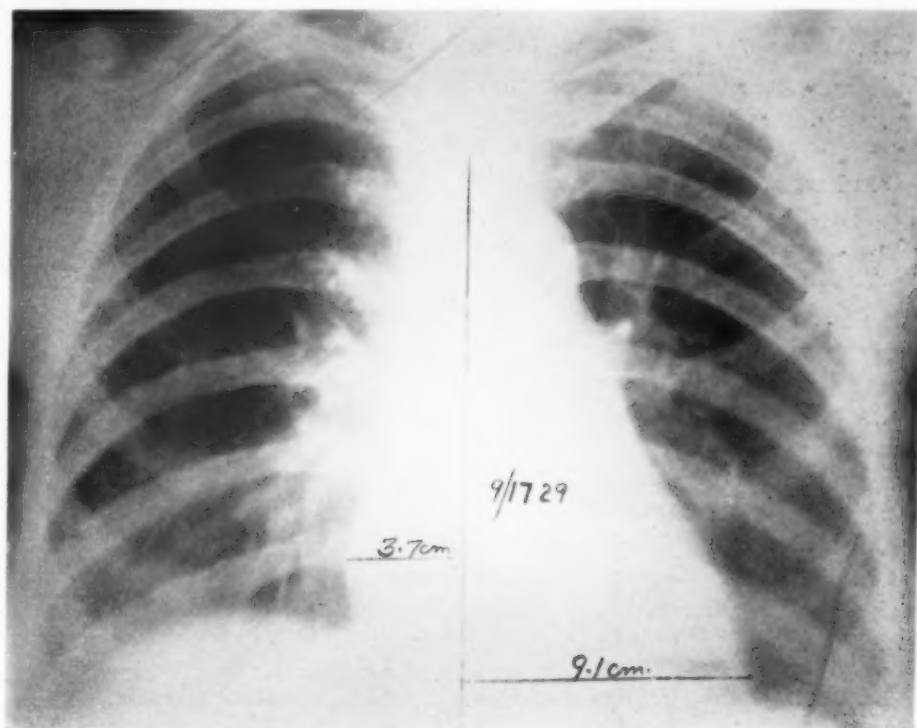


Fig. 2. Six foot plate taken 9/17/29 showing reduction in size of heart after thyroid therapy.

though the symptoms of myxedema disappeared.<sup>4</sup> There are several possibilities here, either the enlarged heart was due to some other cause such as coronary disease or hypertension, or they were not given a sufficiently long time to return to normal. At this clinic it has never been claimed that all myxedemas have myxedema heart any more than one would say that all myxedemas have secondary anemia and nephrosis, nor that it was not possible for an enlarged heart from another cause to coexist with myxedema. Some of our cases have taken two to three times as long as others to return to normal size.

Another result that may be observed is a return to normal of the size of the heart and still not have any marked change in the electrocardiogram. Likewise the patient may have anginal attacks which disappear on thyroid<sup>5</sup>, while others continue to have anginal attacks and a few develop the pain after thyroid medication. Herrick<sup>6</sup> of Chicago, Baron<sup>7</sup> of Minneapolis, and others have noted anginal attacks in people with marked anemias who showed changes in their electrocardiograms. When the blood returned to normal, the attacks of angina ceased, and the abnormalities of the electrocardiogram disappeared. One of Fahr's

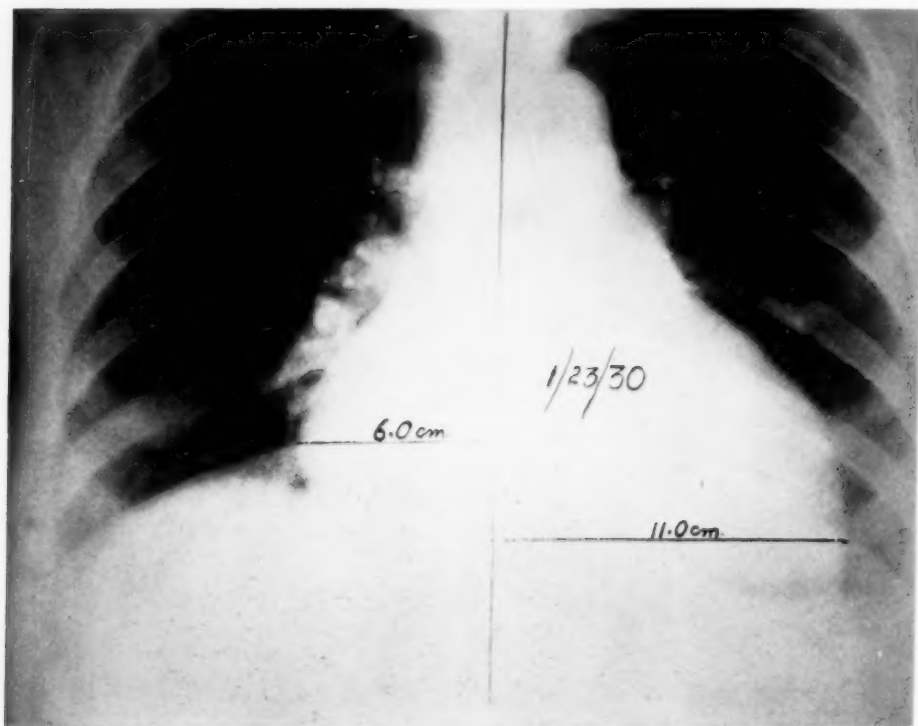


FIG. 3. Six foot plate taken 1/23/30 showing dilatation of the heart after withdrawal of thyroid.

cases showed electrocardiographic evidence of coronary disease which disappeared after thyroid but reappeared six months later and has remained ever since. This is not unexplainable when we consider the following:

It is impossible to predict whether a case will have angina pectoris before or after thyroid therapy and whether it will disappear, remain, or develop after

thyroid medication. The thickness of the walls of the coronary arteries, the amount of control over the size of the coronary lumen through the vagus nerve, the degree of anemia present, the rise or fall of blood pressure, the length of systole, and the velocity of blood flow are all factors that must be considered in these cases. It should not be surprising that a patient with myxe-

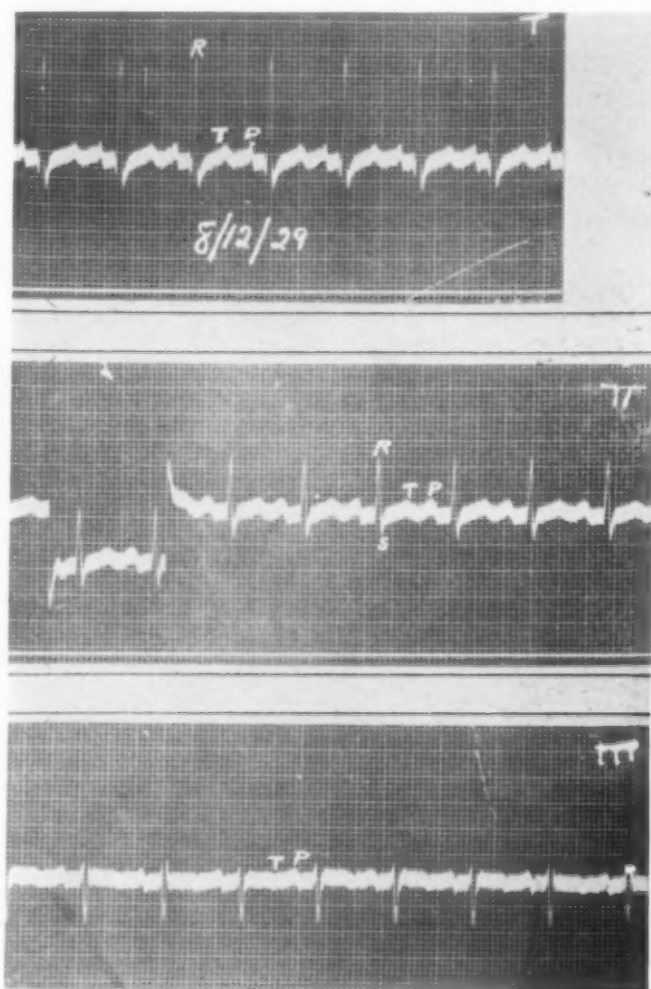


FIG. 4. Electrocardiogram taken 7/12/29 showing very low T waves, PR interval 0.2, negative  $P_2$ .

dema or myxedema heart may have angina attacks that disappear after thyroid medication and it is not impossible to conceive of the pain appearing after thyroid medication on physiological and pathological grounds as well as from purely coincidental causes.

The first cases reported by Zondek had normal blood pressures. All of our

cases have had normal blood pressures although one of them developed hypertension during treatment, which disappeared when the dosage of thyroid was reduced.

A few cases have hypertension<sup>8</sup> at the beginning of treatment, and with the reduction in size of the heart to normal and clearing up of the myxe-

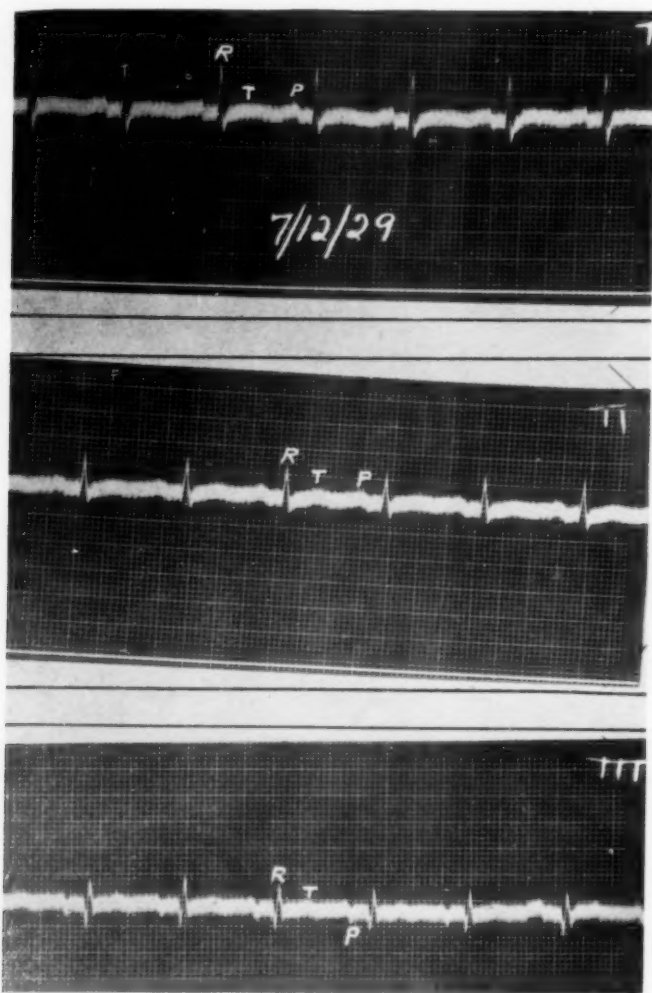


FIG. 5. Electrocardiogram taken 8/12/29 showing definite T and P waves with PR interval 0.2 and a negative QRS<sub>2</sub>. A few weeks later the PR interval became 0.16 and remained there until thyroid medication was stopped.



dema, the blood pressure drops to normal or nearly normal.

Since the appearance of Fahr's paper in this country, several additional cases have been reported by others, but several internists of note claim it is a very rare condition, while a few have even denied its existence. This is difficult for us to understand. Out of 12 cases of myxedema seen in this clinic during the

past five years, nine have had myxedema heart and eight have responded to treatment by a reduction in size. In the one case where we have had a failure, we consider it partly the fault of the patient who would not remain a sufficient length of time in the hospital, and who would not take an adequate amount of thyroid.

Most certainly there are many cases

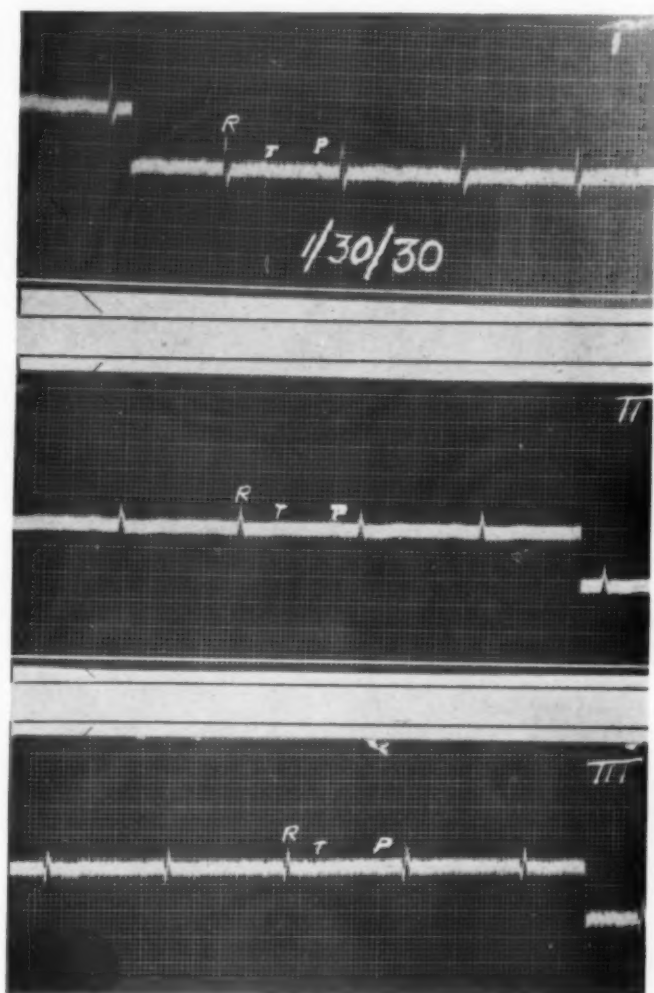


FIG. 6. Electrocardiogram taken 1/30/30 showing iso-electric to very low T and P waves, PR interval of 0.2 to 0.22 and very low potential of QRS in all leads.

of depressed basal rate which are not due to deficiency of the thyroid, only 45% of the basal rate can be accounted for by the thyroid gland. Other glands of internal secretion play a rôle. When we speak of myxedema, we do not speak of a patient with a depressed basal rate, but of those with symptoms and signs of myxedema as well as a depressed rate.

As to the pathology of myxedema heart, it can be said that no definite pathological picture is known.

A question that naturally arises is, how does thyroid act? The best evidence I know of is from work done in Frederick Mueller's<sup>9, 10</sup> laboratory where it has been shown that thyroxin and thyroid extract added to the perfusion fluid of an isolated frog heart causes an increase of the amplitude of the beat.

Some men<sup>11, 12, 13</sup> have sounded a warning on the danger of thyroid treatment in these cases because of putting a strain on a damaged heart by increasing the metabolism. A case has been reported in which death occurred two weeks after the return of the heart to normal size<sup>14</sup>. Another died during treatment, and cardiac infarction was found<sup>15</sup>. One does not have to have myxedema to die of cardiac infarction. The greatest danger to our minds is in not using thyroid, for that is the very drug that cures a myxedema heart. Even if a hypertension should develop, who would not prefer it to myxedema? Hearts that do not respond to thyroid because of other cardiac pathology may be helped by the simultaneous administration of digitalis or euphyllin, just as one might use them in any of the non-myxedema heart failures.

We are now using fresh preparations of Armour's thyroid extract, starting with 1 grain twice a day and gradually increasing to 1 grain five times a day. This dosage is decreased or increased according to the basal metabolic determinations and any untoward or disagreeable symptoms that may arise. In eight cases at this clinic, there have been no deleterious results from thyroid extract. In fact we have seen heart failures clear up, and the patient return to a normal existence. Some of them have been followed for five years, and none of them complained of heart symptoms except when they neglected to take thyroid or took too much. The patient must see a doctor once a month for a check of his pulse rate, basal metabolism, and for an evaluation of his subjective symptoms. In the hands of a doctor, who constantly watches his patient and is competent to evaluate cardio-vascular symptoms, we do not think there is any danger in the use of thyroid extract.

#### SUMMARY

1. Myxedema heart exists and is not uncommon in true myxedema.
2. A case is reported of a 48 year old woman with typical symptoms and signs of myxedema and myxedema heart. Teleröntgenograms and electrocardiograms are presented showing changes before and after thyroid medication as well as following withdrawal of thyroid.
3. In myxedema heart all the symptoms and signs of cardiac decompensation may be found.
4. The majority of myxedema hearts decrease in size on thyroid. On withdrawal of the thyroid extract, the

heart dilates and can again be brought to normal size by thyroid. This result cannot be secured with digitalis.

5. Enlarged hearts in myxedema, that do not decrease in size on thyroid, may be due to coronary disease, hypertension, or other causes.

6. Changes in electrocardiograms are discussed and explanations offered for these changes.

7. Theories to explain attacks of angina are given.

8. No definite pathological picture of myxedema heart is known.

9. The treatment of myxedema heart is discussed.

For references, the reader is advised to see the bibliography at the end of an excellent review of myxedema heart by Holzman, which is given below, together with a few additional references, some of which have appeared since Holzman's paper.

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## Foreign Bodies in the Stomach\*

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THE discovery of foreign bodies in the stomach in the course of roentgenologic investigation or laparotomy is not uncommon. The literature on this subject is extensive and includes case histories describing the discoveries of a most amazing variety of substances retained in the human stomach. Wölfler and Lieblein reviewed 1184 cases of foreign bodies in the stomach and small bowel.

In this paper we shall report ten cases in which operations were performed for foreign body of the stomach, and three other cases contributed by Dr. O. Heyerdale of the State Hospital for the Insane at Rochester, Minnesota. We have not included in this paper the numerous instances in which patients examined at The Mayo Clinic reported that they had swallowed foreign bodies.

### GENERAL CONSIDERATION OF FOREIGN BODIES IN THE STOMACH

The subject of foreign bodies in the stomach may be subdivided into several groups: (1) swallowed objects; (2) foreign bodies formed within the stomach: trichobezoars, trichophyto-

bezoars, phytobezoars and mineral bezoars, and (3) foreign bodies deposited in the stomach from the exterior, through surgical or violent wounds or from adjacent organs through fistulas, such as gallstones.

*Swallowed Objects*—Children frequently swallow small objects such as needles, pins and screws. Small, blunt objects which reach the stomach are frequently passed through the intestinal tract without much difficulty. Needles are more likely to cause abscess and perforation, especially if an emetic is given. Occasionally needles that have been swallowed will be found in parts considerably removed from the stomach or intestine, such as the region of the knee<sup>7</sup>, or in the thorax<sup>5</sup>.

Wölfler and Lieblein found that in about 25 per cent of instances, such objects as knives, forks and spoons found their way out through the rectum without seriously injuring the bowel or causing other complications such as obstruction. The longer and sharper these objects, the greater is the danger of perforation. Moreover, an object that lies obliquely to the long axis of the viscus is more likely to cause perforation during peristalsis.

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Even blunt objects may cause ulcers or perforation.

*Bezoars*—A bezoar is a calculus or concretion found in the stomach or intestines of some animals, formed of concentric layers of mineral, vegetable or animal matter deposited around some foreign substance which serves as a nucleus. In medical literature, almost any type of foreign body in the stomach is termed a bezoar. There is much evidence to suggest that the word has its origin either in the Persian word "pad-zahr" or perhaps in the Arabian word "bezahr."

The Persian word "pad-zahr" is divisible into two words "pad" meaning "counter" and "zahr" poison, thus an antidote for poisons. Substances found in the entrails of animals, even to modern times, were considered as antidotes for various poisons. These bezoars were highly prized because, not only was it assumed that they had intrinsic value as curative agents, but mystical powers were ascribed to them so that they were worn as charms to ward off diseases. In the seventeenth century it was written<sup>4</sup>: "The bezoartick is the present cure for all poysons and feaners. Extracts were also made and taken as medicines to cure various diseases. The most commonly found bezoars are the phytobezoars (plant-bezoars) which are built up mainly of vegetable matter; the indigestible substances of foods, such as seeds and fibers, are the structures around which most of these bodies are formed. The literature includes numerous cases in which patients have drunk paint or varnish in order to get the effect of its alcohol content. The included shellac in

some instances would act as a binding substance on the vegetable contents of the stomach, forming a foreign body which would fail to pass out of that organ. There are other instances in which the shellac alone formed a rather firm foreign body within the stomach, the tumor at times assuming large proportions.

Probably the most frequent source of gastric bezoars in the United States is the persimmon. The sticky juice and pulp of this fruit have a high content of pectin and gum, and it is probably because of this that bezoars occasionally develop following the ingestion of unripe persimmon.

Some solid concretions found in the gastro-intestinal tract are formed mainly by salts of calcium and magnesium. These are found more frequently in the small intestine than in the stomach. Occasionally they become large and may lead to serious complications such as obstruction or perforation.

A trichobezoar is a foreign body made up largely of hair. If this contains, as it usually does, vegetable matter, it is called a trichophytobezoar. The habit of some nervous or hysterical patients of swallowing hair occasionally results in the development of hair-balls in the stomach. These usually take the shape of the stomach. It is extremely unusual that hair-balls are found in the intestines, although a prolongation of the intragastric strands of hair may extend into the duodenum. The size of these accumulations of hair may be remarkable. The literature includes an instance in which a hair-ball weighed five pounds<sup>5</sup>. Frequently these accumulations cause marked dilatation of the stomach. The gastric wall may be thin,

and occasionally there is an associated gastric ulcer. The tumors are usually hard, due to the consistent packing together of the swallowed hair, and due also to the fact that detritus of all sorts becomes enmeshed in the hair-ball.

*Foreign Bodies Entering the Stomach Through Fistulas, or Puncture Wounds, and Those Left in the Gastro-Intestinal Tract Following Operation*—The development of fistula between the biliary duct system or the gall-bladder and the stomach may result in the appearance of a gallstone in the stomach. Such fistulas are much less common than those connecting the gallbladder or bile duct and the duodenum.

Occasionally these gallstones will cause intestinal obstruction. A drainage or feeding tube may drop into the stomach through an external fistula. This, however, usually passes through the intestinal canal without untoward result.

Occasionally a sponge, a probe or some instrument used during surgical operation may be left in the stomach.

#### SYMPTOMS OF FOREIGN BODY IN THE STOMACH

Even large or sharp objects may remain in the stomach for months or years without causing any complaints. The development of symptoms following the swallowing of foreign bodies, or subsequent to their development within the stomach or bowel, depends largely on their consistence, contour, shape, size and position. These symptoms are divisible into several groups.

*General Symptoms*—Occasionally there is complete collapse, or in chil-

dren convulsions, following the swallowing of large objects. In others there is only a feeling of discomfort or a sensation of epigastric fullness. The appetite may become capricious or may be totally wanting. Diarrhea may become a troublesome symptom.

*Symptoms Arising Secondary to Presence of Large Foreign Bodies*—Foreign body may lead to weakness, loss of weight and strength, dehydration and anemia.

*Disturbances of Motility*—The flatulence, pain, nausea and regurgitation complained of by some patients are attributable to disturbances of the normal gastric motility. There may be marked delay in the emptying time of the stomach.

*Absorption of Poisonous Substances From Swallowed Objects*—Enough copper or lead may be absorbed from foreign bodies to give definite symptoms of metallic poisoning. This has been noticed especially in children who have swallowed copper or lead objects.

*Development of Gastritis or Ulceration*—Gastritis or gastric ulcer may develop in the presence of a foreign body in the stomach. The usual syndrome of ulcer may then be included in the complaints. There is, as a rule, more gas and bloating than in the usual uncomplicated type of ulcer; this perhaps is due to the frequently associated gastritis or the subacute condition of the ulcer. Here, as in other instances of complicated ulcers, the syndrome is likely to be perverted by the association of much flatulence which usually, however, comes on during the time that the pain of ulcer arises, and



is frequently relieved by the ingestion of small amounts of food or soda.

*Hemorrhage*—Sharp objects may produce hemorrhage because of the actual incision of the gastric or intestinal wall. Hemorrhage may also occur as one of the complications of the gastric ulcer which is so often found associated with the foreign body.

*Penetration and Perforation*—Sharp objects may become stuck in the wall of the stomach or bowel, producing severe pains. Other objects, through repeated peristaltic efforts, may be pushed into the wall of the bowel, imbedding themselves therein, or even perforating through into the abdominal cavity. On the other hand, perforation may follow erosion of the gastric ulcer which is so often found associated with foreign bodies. Severe pain and increasing abdominal rigidity should suggest this complication. The symptoms of local or general peritonitis may develop.

*Abscess Formation* — Occasionally erupted ulcers, or objects pushing into or through the wall of the viscus, will result in the formation of abscesses. The symptoms which suggest localized peritonitis then will develop and there will be the systemic reaction which abscesses anywhere will produce, such as pain, malaise, fever and leukocytosis.

*Obstruction*—It is conceivable that many foreign bodies produce some delay in the emptying of the stomach or intestinal tract, producing constipation and a good deal of fullness and abdominal distension. It has been pointed out that occasionally diarrhea develops; this is probably due to enteritis or

gastritis. Constipation is more likely to be present than diarrhea. With increasing obstruction the symptoms become more definite, there being more distention and increasing difficulty in obtaining normal bowel movements. Complete obstruction at the pylorus due to a foreign body is not common, however, occasionally foreign bodies such as gallstones will cause a complete obstruction in the small bowel. The symptoms of acute obstruction are well marked and usually do not present great difficulties in diagnosis.

#### DIAGNOSIS

A carefully taken history frequently helps greatly in making a diagnosis. In mentally defective patients, a history of swallowing one object should lead to the suspicion that other objects have been swallowed previously. The development, then, of gastro-intestinal symptoms of any nature should promptly lead to careful investigation with that in view.

In children who are known to be swallowers of hair the possibility of a hair-ball must always be borne in mind in evaluating symptoms of a gastro-intestinal disturbance.

The ingestion of large amounts of persimmons or of other fruits containing large amounts of gum and resin should lead to the suspicion of the possibility of phytobezoars.

Occasionally the discovery of foreign bodies passed by rectum in cases in which the complaint is referable to the gastro-intestinal tract will lead to the correct diagnosis. No definite syndrome is characteristic of any of the foreign bodies of the stomach. The frequent association of gastric ulcer in

such cases makes the symptoms of this complication more likely to occur than in any other one syndrome.

Freely displaceable tumors in the epigastrium, which are not particularly tender, may lead to the diagnosis of foreign body. Sometimes two tumors of similar consistence, and apparently with similar general characteristics, are palpable. This again should suggest the probability of foreign bodies. Large, displaceable tumors in the epigastrium, such as those caused by hair-balls, occasionally because of their physical characteristics, aided of course by the history of hair swallowing, make possible the diagnosis of this condition preoperatively.

By far the most important aid in the diagnosis of such a condition is the roentgen ray. Usually even semi-opaque objects and even hair-balls can be discovered. The discovery of obstructed regions may also be a help in localizing foreign bodies which are causing definite symptoms.

Laparotomy is often advised in these cases because of an indeterminate type of mass or because of an indeterminate type of obstruction caused by one of these foreign bodies, and this is not infrequently the only way of being absolutely certain of the type of lesion with which one is dealing.

#### REPORT OF CASES

*Case 1*—A man, aged forty-eight years, two and a half months before admission to the clinic, while on a long walk in the woods of Indiana, ate a large quantity of persimmons. On the basis of this history, the symptoms, and the general examination, a diagnosis was made of persimmon bezoar. As far as we know, this is the first case of persimmon bezoar that has been diagnosed before roentgenologic examination or opera-

tion. The case has been reported, with stress on the roentgenologic aspects, by Camp.

*Case 2*—A man, aged twenty-four years, while hunting, ate about a quart of persimmons. A persimmon bezoar resulted. The case has been reported by Balfour and Good.

*Case 3*—A man, aged thirty-seven years, who was accustomed to eating large quantities of persimmons while playing golf in Mississippi complained of gastric distress. Two persimmon bezoars were removed from his stomach at one operation. The case has been reported by Droegemueller.

*Case 4*—A woman, aged thirty-two years, had been in state asylums for nervous and mental disease three times because of temporary insanity. There was no history of any previous illnesses of significance. The patient entered the clinic complaining that at intervals of several months she had had attacks of sudden, severe pain in the epigastrium. The attacks lasted about two weeks and were accompanied by nausea, vomiting and occasionally by fever. The pain was often referred over the entire abdomen, but the maximal distress was on the left side below the margin of the ribs. Apparently she had not lost weight, and at the time of examination she appeared to be sane.

There was a freely movable mass in the left upper part of the abdomen. Roentgenologic investigation of the colon gave evidence of redundancy of the transverse colon and sigmoid; nothing else of significance was found. Because of the possibility that the mass found on examination might be kidney, cystoscopic examination was done and pyelograms were taken, but results were negative. It was thought that the mass might be a floating spleen, and operation was advised.

At operation a trichobezoar weighing 240 gm. was found in the stomach. It was 25 cm. in length and was made up of hay, hair, strings and cloth (Fig. 1). Its removal was followed by an uneventful recovery.

*Case 5*—A woman, aged thirty-three years, came to the clinic complaining of an abdominal tumor and loss of strength and weight. Two months before, the patient had noted a tumor in the upper part of the ab-

domen, the size of "a small orange," which could be shifted from side to side. Two to three weeks before registration she began having upper abdominal cramps lasting from a few minutes to half an hour. She was constipated and this trouble was increasing. Occasionally she had nausea and vomiting but no other gastric distress. There was no bleeding from the bowel, and no hematemesis. A roentgenogram of the stomach gave evidence of a large ulcer of the lesser curvature at the angle, probably malignant; there was marked obstruction. A diagnosis of extensive carcinoma of the stomach and marked secondary anemia was made.

Exploration revealed normal gastric walls except for changes characteristic of gastric ulcer, and a large tumor. To mobilize the stomach was difficult because the gastric ulcer was attached to the liver. The ulcer

was exposed through a large opening in the gastrocolic omentum. From the extent of it, an inoperable tumor was suspected, probably a lymphosarcoma. On continued palpation, the tumor was found to be rather doughy and because of the fact that very few nodes were involved, the stomach was opened and a hair-ball was removed. The crater of the ulcer was about 4 cm. in diameter, and it was considered that it might be malignant. Because of the condition of the patient and the condition of the tissues, it was thought best to close the opening, give medical treatment and allow the patient to go home for a month or two.

A letter dated January 10, 1928, from a friend of the patient stated that the patient was perfectly well, eating all kinds of food without gastric distress.



FIG. 1. Gastric bezoar, consisting of hair, string and cloth. It was 25 cm. long and weighed 240 gm.

*Case 6*—A girl came to the clinic complaining of constipation, and of an abdominal tumor that had been noted two weeks before. She had been well until about ten days before, when she had a "bilious attack," headache, constipation, drowsiness, and slight fever. That same evening she noticed some abdominal pain. The next evening she was nauseated after eating greens. Then generalized cramp-like pain through the abdomen developed. She went to bed for one day. She gave a history of being restless at night and of pulling and chewing hair.

General examination revealed a large, freely movable abdominal mass. The mass was irregular; crepitation was elicited, and it was easily displaced to any part of the abdomen. A cyst was suspected and operation was advised.

A large hair-ball that almost filled the stomach was removed.

*Case 7*—A man, aged fifty-one years, came to the clinic complaining of "heart

burn" and vomiting of all foods, of six months' duration. Six months before admission he had had a rather sudden burning sensation at xiphoid process, with radiation to the right of the sternum and up into the neck. He seemed to fill up to the xiphoid region and then would vomit. When this difficulty was first noticed he had as much trouble with liquids as with solid foods. He would be free from trouble for a few days and then attacks would come on again. The last attack had continued for three weeks. He had lost about 7 pounds in weight. He had had no trouble with his stomach since an operation for ulcer seven years previously. He did not know exactly what had been done at this operation.

Roentgenologic examination gave evidence of cardiospasm with slight dilatation of the esophagus. There was deformity of the duodenum, probably due to plastic operation. On bronchoscopic examination there was no obstruction to a number 41 French olive-tipped



FIG. 2. Gastric hair-ball that took the form of the stomach. It measured 14, 12 and 6 cm. in various dimensions and weighed 800 gm.

bougie. The thread broke when an attempt was made to pass a number 55 French sound. Three days later a number 55 French sound was passed, with a moderate amount of pain. Eight days later the patient seemed to be relieved of all trouble. Roentgenologic examination of the esophagus then was negative. He was advised to return if he had more trouble.

The patient was readmitted five months later with approximately the same complaints as before. He was completely relieved by dilatation of the cardia and was dismissed.

Five months later, roentgenologic examination of the esophagus gave practically

negative results. One year later the patient's chief complaint was cramps in the stomach of four months' to one year's duration. He had been kept in bed for two months. The pain came on at intervals and was usually more severe from half to one hour after eating, and at night. He stated that for three months he had vomited practically everything he ate. The food seemed to stick in the midthoracic region and in the region of the cardia, and then to slide through into the stomach. He seldom vomited water. He had lost 10 pounds in weight in four months. He took a cathartic every two days. He had to urinate three or four times each night for two months.



FIG. 3. Gastric ulcer associated with the hair-ball shown in Fig. 2.

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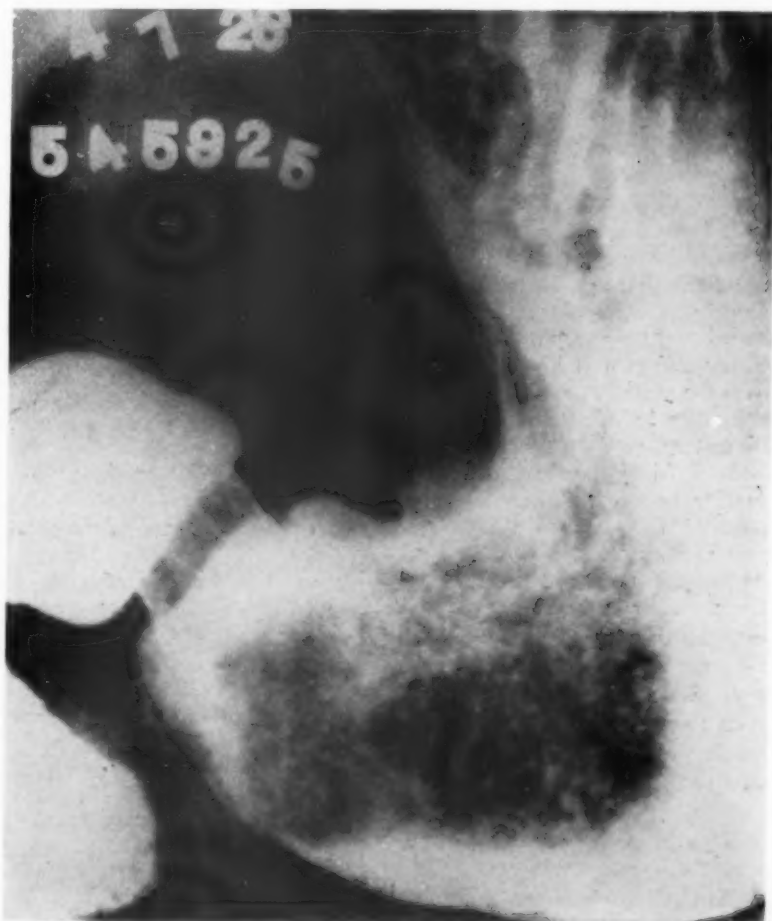


FIG. 3. Gastric ulcer associated with the hair-ball shown in Fig. 2.

On examination of the abdomen, definite peristaltic and anti-peristaltic movements could be seen synchronous with the patient's cramps. An irregular mass was palpable. Roentgenologic examination of the esophagus and stomach gave evidence of obstruction at the cardia, apparently malignant. There was duodenal obstruction 15 cm. from the pylorus; the opening made at gastro-enterostomy was not free. Esophagoscopy examination gave negative results.

Exploration of the stomach and duodenum was performed eight days after admission. An operative diagnosis was made of foreign body (fish line) in the stomach, pyloric obstruction, jejunal ulcer, subacute duodenal ulcer, and partial obstruction of the gastro-enterostomy opening. The patient had a large stomach and duodenum with a subacute, contracting type of lesion almost immediately below the pylorus. In the stomach itself was a mass about 5 by 6.5 cm. lying near the small posterior gastro-enterostomy opening. This felt like a foreign body and was rather suspected of being twine before it was opened because of the fact that the twine had broken during one of the dilatations of the cardia more than a year previously. The strands of twine extended down into a long proximal loop. On the mesenteric side of this loop about 8 or 10 cm. from the gastro-enterostomy opening was a perforating lesion with rather extensive inflammatory products about it, but which was certainly not carcinoma. It seemed best to remove the mass of twine which extended not only to the gastro-enterostomy opening but down through the pylorus so that the strand had to be divided before the mass could be removed. The gastro-enterostomy was taken down, the openings in the stomach were closed, the duodenal ulcer was excised and a plastic operation on the outlet of the stomach was performed. It was thought that the jejunal ulcer would probably heal, since the gastro-enterostomy had been disconnected. On account of the size of the stomach and the situation of the openings, the cardia could not be explored. Everything appeared to be in good condition at the completion of the operation. The pathologist's report on tissue

removed from the pylorus was "inflammatory hypertrophy."

Three weeks later the wound was completely healed and the patient felt well. He could eat well and had no indigestion or dysphagia.

*Case 8*—A young married woman came to the clinic because of an attack of nausea, vomiting and pain, with exacerbations of severe pain in the lower right quadrant of the abdomen. Soreness and pain occasionally radiated through to the back. Two years later the patient returned to the clinic complaining of spells of vomiting, regurgitation before and after meals of a greenish-yellow, bitter fluid, and on several occasions of particles of undigested food. Dizziness always preceded vomiting; menstruation made the vomiting worse.

Function of the bowels was normal and the appetite was good. Before vomiting, the patient would have a sharp knife-like pain in the left side. She thought she noticed some jaundice after vomiting. The pain was rather indefinitely situated.

On exploration a perforated duodenal ulcer about 4 cm. in diameter was found. It was buried in adhesions, was situated about 6 cm. below the pylorus, and one point of a wooden toothpick was in the ulcer and the other projected into the stomach. The upper part of the abdomen was filled with adhesions. Chronic appendicitis was present.

*Case 9*—A girl, aged six years, was brought to the clinic with dysphagia due to cicatricial constriction. Four years before, while eating an apple, the patient had dropped it into some liquid lye, had picked it up again and had continued to eat it.

At the time of examination at the clinic, the patient was able to swallow milk. The esophagus was dilated at monthly intervals for four months because of cicatricial stenosis. About a month after registration, when an attempt was made to dilate the esophagus, a number 22 French sound did not go completely through. During the second dilatation the thread broke before the operation was completed. The third dilatation was done under anesthesia. At the last dilatation a number 30 French sound was used without cutting. The whalebone staff and spiral tip

separated, leaving the tip and a number 28 or 30 French long spindle between the two strictures.

A Witzel gastrostomy was done and the olive and about 7.5 cm. of the whalebone staff were removed through the opening on the anterior surface of the stomach. The opening was sutured with two layers of chromic catgut. The new opening was left just large enough for a catheter to be inserted.

*Case 10*—A woman, aged twenty-three years, was an inmate of the Rochester State Hospital because of dementia praecox.

September 22, 1915, the patient was operated on at The Mayo Clinic. Seven teaspoons, a hair pin, a straw and some hair were removed from the stomach. The case has been reported by Balfour.

For the following three reports of cases we are indebted to Dr. O. Heyerdale of the Rochester State Hospital.

*Case 12*—A man, aged fifty years, affected with a manic depressive type of psychosis, swallowed hair pins, bolts and nuts. Finally the patient began to complain of abdominal pain, distress and constipation, and he became rundown physically.

The patient was put to bed on a diet chiefly of oatmeal and soft foods, and passed a large number of these objects. After passing numerous bolts and so forth, he felt relieved and was dismissed from the infirmary. The patient occasionally swallowed more foreign bodies, mainly bolts, and after a few months he was again hospitalized and the previous treatment was again instituted. This procedure has been repeated three or four times.

*Case 13*—A man, aged thirty-four years, was a victim of a manic depressive type of psychosis.

The patient scraped out with a knife the edible portion of a squash until only the

hard rind remained. This he rolled up tightly into a cigar-like mass. He managed to push this mass into his stomach. For some time he had no untoward symptoms. Weeks later, epigastric pains developed. At one time he vomited blood. Soon after these symptoms began he died rather suddenly.

Necropsy disclosed that the rind had sawed a hole through the gastric wall, producing hemorrhage and fatal peritonitis.

*Case 14*—A man, aged forty-five years, who had a manic depressive type of psychosis, broke a wire from the bed spring and swallowed it. The wire was in the shape of the letter T. He was given a diet of oatmeal and soft food and within a few days he passed the swallowed body by rectum. He apparently suffered no untoward effects from the experience.

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## Chronic Sinus Infection in Relation to Systemic Disease\*†

By NOBLE W. JONES AND FRANK B. KISTNER, *Portland, Oregon*

WHEN one refers to chronic hyperplastic sinusitis, and especially to the non-purulent form of chronic hyperplastic sinusitis, as a focal infection of importance, one treads upon debatable ground. Many rhinologists of note believe that chronic inflammation of the nasal accessory sinuses plays little, if any, role in the causation of systemic disease<sup>1</sup>. Although our work during the past five years has led us to other conclu-

sions, yet we have respected these views, and they have, we believe, tempered our enthusiasm and have influenced the forming of our opinions.

The work now presented has been gleaned from an unfinished analysis of about 750 patients upon whom radical sinus operations have been performed for varying diseased states. The patients group themselves into more or less well defined entities, such as anemia, arthritis, bronchitis and asthma, cardio-sclerosis, general malaise, and a neurological group consisting of chorea, spasmodic tic, periodic hyperpnea, etc. We shall illustrate these different groups of diseases by short case histories, and discuss the underlying pathology and bacteriology of the diseased sinus tissues and the animal experiments made with them.

*Group 1. Chronic Bronchitis and Asthma.* More patients suffering from chronic sinus disease fall into this category than into any of the other groups. Bronchitis may exist alone; secondary bronchitis—asthma may also develop later in patients in whom there is no evidence of allergy; and, furthermore, still other patients, having a pre-existing hay fever, may seemingly develop a bronchial asthma upon their allergic basis aided or accompanied by a sinus bronchitis.

\*(Abstract of clinic held February 14, 1930, at the Fourteenth Annual Clinical Session of the American College of Physicians, Minneapolis, Minnesota.)

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<sup>1</sup>Shambaugh (*Jour. Am. Dent. Assn.*, Vol. 16, 5, May, 1929, pp. 773-781) for instance says:

"Regarding the question of sinus disease as a focus for systemic infection, I am of the conviction that chronic sinus disease is a much less important factor in producing infection than are either the teeth or the tonsils. ...

"A demonstrable sinus infection occurring in connection with systemic disease appears to be extremely rare. ...

"I have been interested in the problem of focal infection since these studies first began, but I have seen few patients in whom there appeared to be any justifiable suspicion that chronic sinus disease was a factor in producing a systemic infection."

*Case 1.* BB, age 13, April, 1928. Chronic bronchitis began in this patient with acute colds before two years of age. The child has never been free of it. Seven times she has had pneumonia; three times the pneumonia was diagnosed lobar, the child having bloody sputum and the pneumonia lasting about nine days, and ending with crisis. She expectorates half an ounce of purulent sputum each day. Examination showed bilateral coarse râles and rhonchi with thickening of the peribronchial shadows in the lower lobes of the lungs. There was no evidence of tuberculosis. Tonsils and adenoids had been previously removed. There was present a generalized pan-sinusitis. On April 7, 1928, a double radical antrum operation was performed. Free pus was found in both antra. The linings were uniformly thick, red and edematous (Fig. 7). The posterior ethmoid cells were opened from the antra on both sides. On May 7, 1928, there was a right frontal, ethmoid and sphenoid operation, and a left intra-nasal ethmoid operation performed. Free pus was found in all of the sinuses, together with polyp formation.

Cultures from swabs and tissues from the right antrum gave colonies of staphylococcus aureus, alpha hemolytic short chain strepto-

cocci, and long chain beta hemolytic streptococci. Swabs and tissue cultures from the left antrum gave staphylococcus albus, alpha hemolytic and beta hemolytic streptococci.

Through the summer the cough and expectoration disappeared. The patient had had much operative work done upon her head. At 9 years of age she had had a mastoid operation which healed successfully. At the age of 3 years her tonsils and adenoids had been removed cleanly. In November, 1926, both antrums had been opened and washed for a month, and in July, 1927, polypi had been removed from the right antrum intranasally. These temporizing operations upon the sinuses had had no effect whatsoever upon the progress of the chronic bronchitis.

*Case 2.* R.L.G., age 54, April, 1923. The patient, who at the present time has a severe asthma, has been of special interest to us, for during years of observation we have seen a chronic asthma develop in one in whom there has been no evidence of allergy. It began, and recurred intermittently, with acute cold infections. At first merely a mild rhinitis appeared. Later polypoid swelling in the posterior ethmoid and sphenoid regions, which disappeared as soon as the acute colds were over, occurred. As re-infection took



FIG. 1. Shows the method of exenterating the antral membrane.

place the growth of polyps throughout these regions and in both antra progressed to the point where massive polyp formation existed in both antra, and at the same time the asthma became protracted. There has been no radical operative work done upon this patient. Temporizing efforts have been made to give him relief by the periodic removal of some of the larger polyps and by the use of a vaccine prepared from cultures. The importance of this case to us has been watching the evolution of a severe bronchial asthma, not associated with allergy, but associated with the development and progression of a chronic hyperplastic sinusitis.

*Case 3.* Mrs. TMB, age 62, May, 1927. This patient has suffered severely from asthma for 6 years. Exacerbations are re-

lated to head colds and are not related to seasonal changes. Hay fever has also been present for 10 years. Attacks begin in July and continue through August, the patient being free from these symptoms for the balance of the year. She is sensitive to reed canary grass, squirrel tail, red top, alder and aspen. Relief from the hay fever has been obtained by going to the sea shore. A general asthenia with much loss of weight has accompanied the asthma. The right antrum contained a purulent hyperplastic membrane with polyp formation. The left antrum had a smooth, generalized thickening of the membrane, and was half full of viscid mucoid material. The ethmoids and sphenoids were also involved. On June 10, 1927, a double radical antrum operation was per-

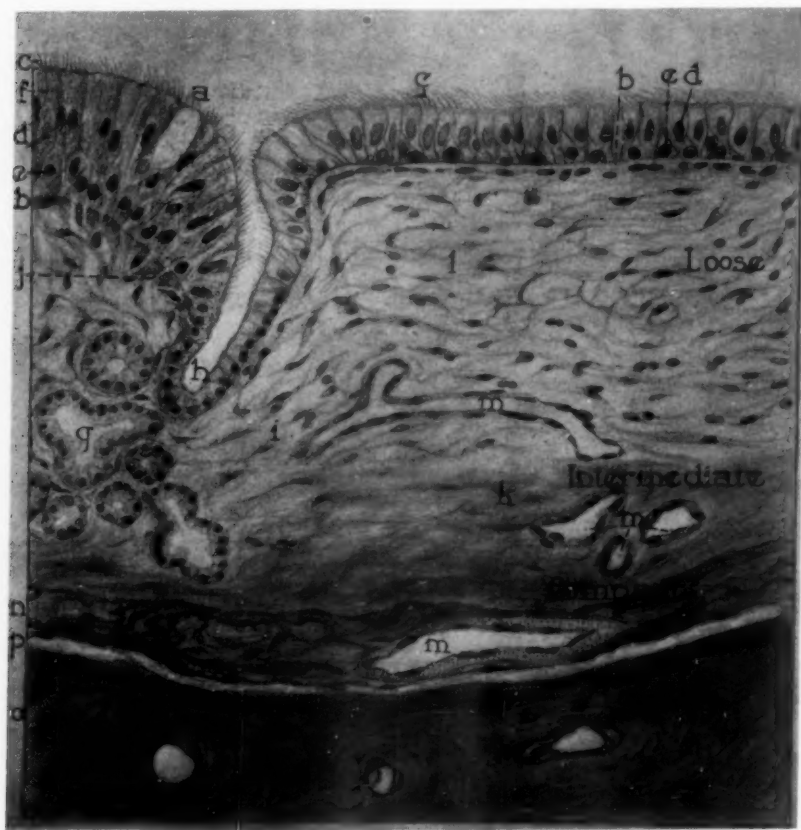


FIG. 2. Diagrammatic drawing of the normal sinus membrane.



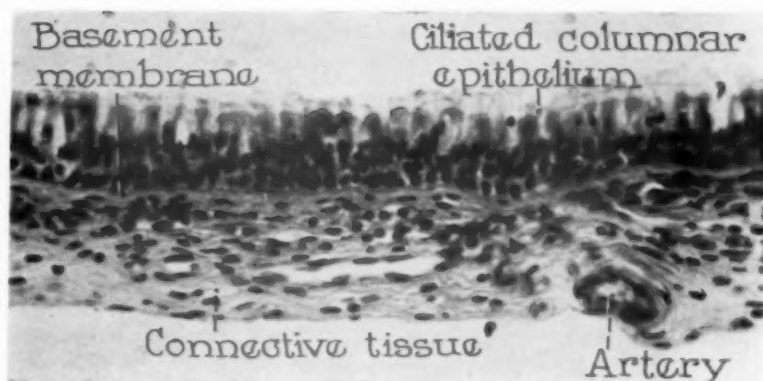


FIG. 3

FIGS. 3 and 4. Microphotographs of normal and diseased sections of ethmoid membrane taken from locations as shown in Fig. 5—which is drawn to scale.

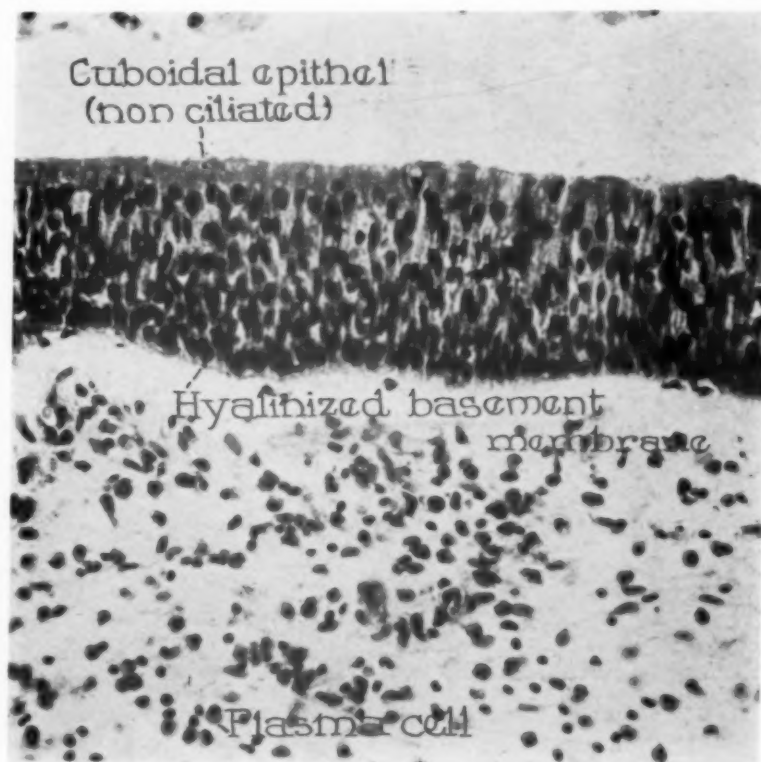


FIG. 4

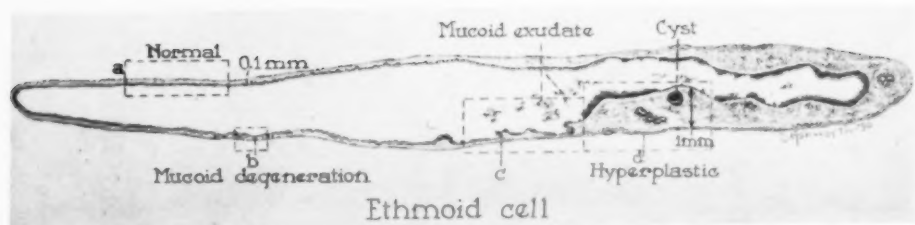


FIG. 5

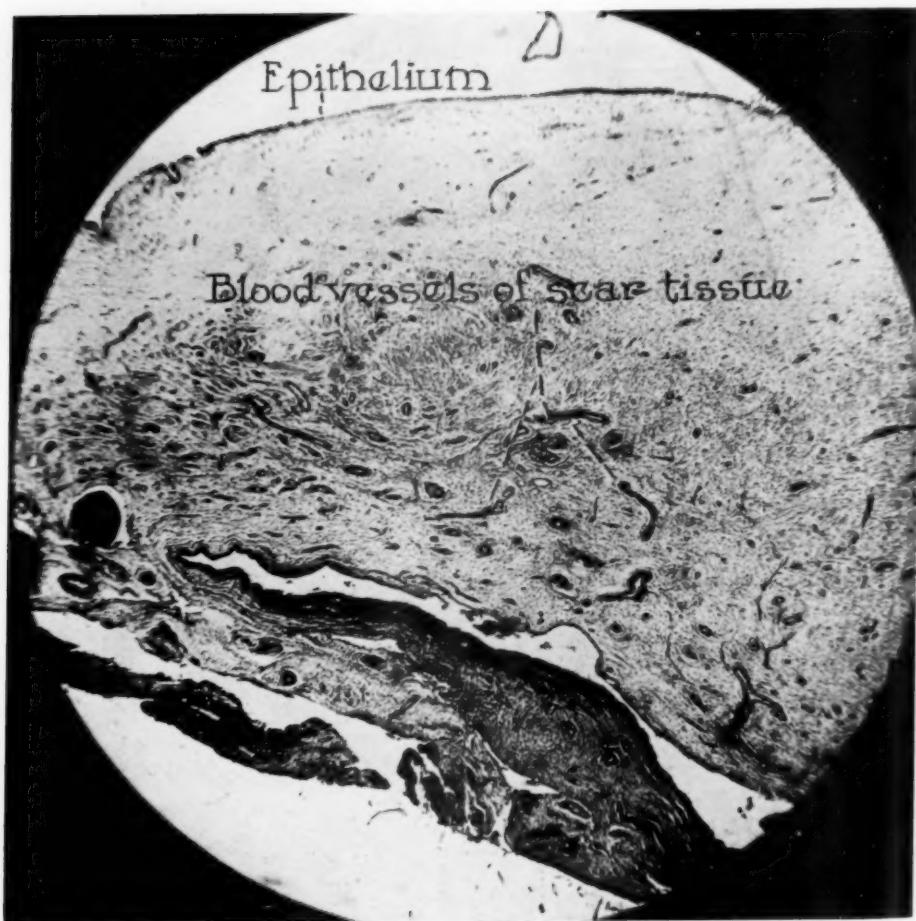


FIG. 6. Microphotograph of section of healed antrum tissue—showing single layer of non-ciliated columnar epithelium and thick layer of scar tissue with fibroblasts and many newly and irregularly formed blood vessels. This portion of the diseased tissue had been removed intranasally two years before the present trans-antral operation.

formed, and on June 28, 1927, an intra-nasal ethmoid and sphenoid operation. Hyperplastic tissue, filling most of the ethmoid cells and both right and left sphenoids with free pus, was removed.

The patient was free from asthma until the spring of 1929, when it slowly returned, beginning with hay fever in May, associated with fever and a return of her head colds. October 21, 1929, a trans-frontal ethmo-sphenoidectomy was performed. There was pronounced polypoid thickening throughout the frontals and the anterior ethmoid cells which had not been reached through the intra-nasal route. The previously operated upon sinuses showed complete and satisfactory healing. Relief was again obtained from the asthma, but the patient is now being immunized with a vaccine obtained from the tissue removed at the last operation. *Pathological Report*: The right antrum—the wall is 2-3 mm. thick and regular. The epithelium

is intact and of the pseudo-stratified columnar type and only moderately hyperplastic. The submucosa is greatly edematous and is densely infiltrated with wandering cells in which eosinophiles predominate. The remainder are mostly plasma cells and lymphoid cells. The infiltration decreases as the periosteum is approached. The left antrum—the wall is 2 mm. thick. Microscopically it is similar to that of the right with certain exceptions. The epithelium of the mucosa has undergone mucoid degeneration and it takes a deep blue stain with hematoxylin. The same eosinophilic infiltration is present and there are also dense infiltrations of lymphoid cells.

Cultures from the tissues showed numerous beta hemolytic streptococci and a gram positive diplococcus. A rabbit inoculated with these mixed cultures and autopsied in 72 hours showed in the heart's blood and several joints beta hemolytic streptococci

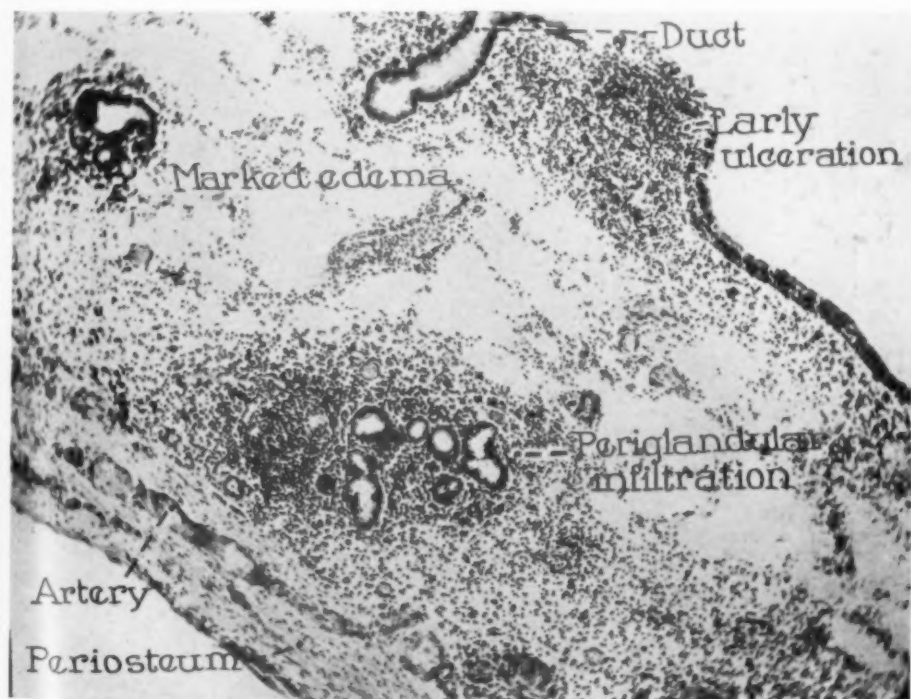


FIG. 7 Microphotograph of section of antrum membrane removed from patient—Case No. 1—bronchitis group.

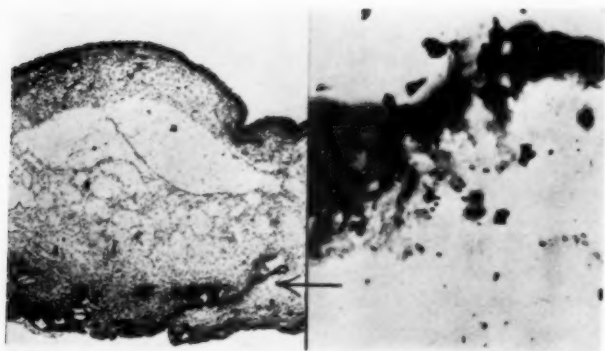


FIG. 8. Microphotographs of sections of antrum membrane removed from patient—Case No. 3—arthritis group. Left shows hyperplasia of mucosa, edema and infiltration of submucosal layers. Arrow points to site of diplococci shown on right.

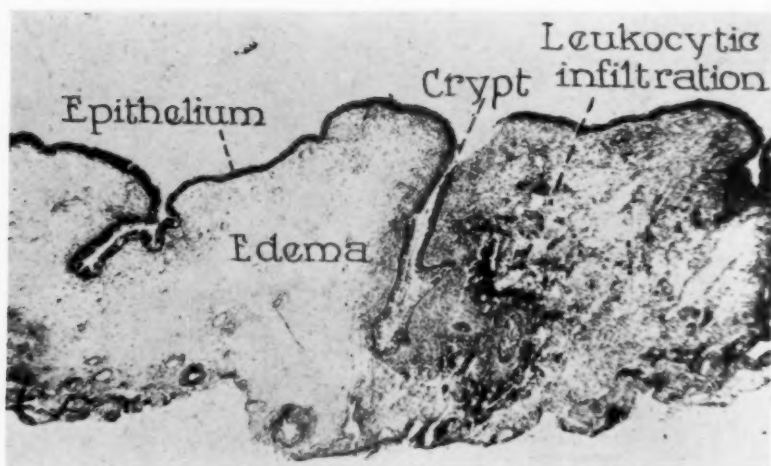


FIG. 9. Microphotograph of section from a different portion of antrum membrane from same patient as in Fig. 8.

and a few gram positive diplococci. A stool culture November 4, 1929, in blood agar media showed many colonies of non-hemolytic diplococci and a few colonies of hemolytic streptococci.

*Case 4.* Mrs. GT, age 35. August, 1929. The patient has suffered severe attacks of asthma since an attack of influenza 8 months ago. Exacerbations have followed acute cold taking without regard to season. Examination showed a non-purulent, hyperplastic, generalized sinus disease. August 30th a double radical antrum and a trans-antral ethmo-sphenoidectomy of both sides was performed, with immediate relief. There was marked thickening of the lining membranes throughout, with large polyps within each antrum. There was no free pus. Cultures from the right and left antrums and sphenoids showed a moderate growth of

green-producing streptococci with a few colonies of staphylococcus albus. A rabbit inoculated with the 24-hour broth cultures was autopsied 48 hours later and showed no distinctive pathological lesions.

Late in December, 1929, following an acute head cold there was a slight return of the asthma. Some pus flakes were washed from the left antrum and a few granulations within the right sphenoid area were cauterized. Stool cultures were made which gave many colonies of a non-hemolytic diplococcus and numerous colonies of a green-producing streptococcus. Complement fixation with the non-hemolytic diplococcus was +4; with the green-producing streptococcus was +1. A sensitized vaccine filtrate was prepared from the two organisms. The subcutaneous injection of .002 cc. of this vaccine produced a reaction characterized by a

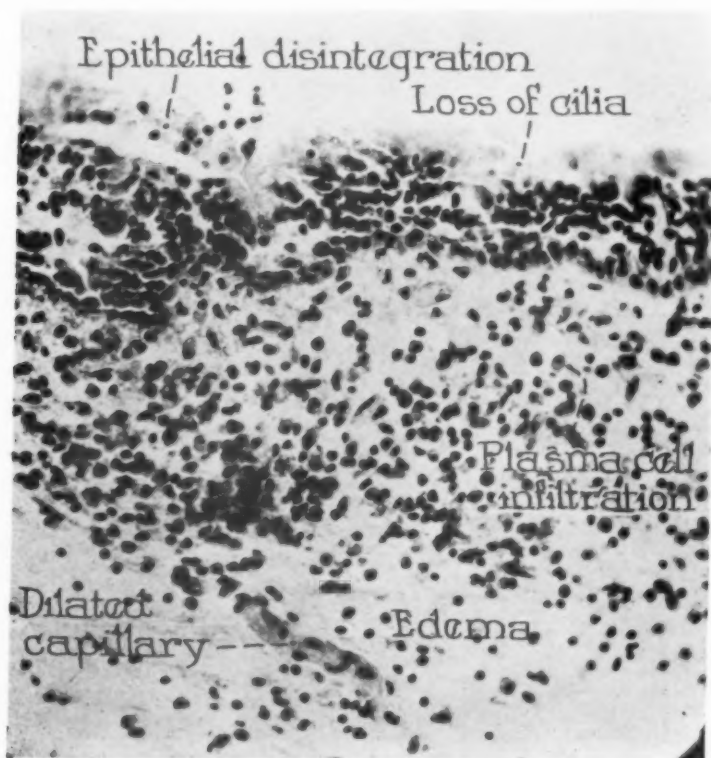


FIG. 10. Microphotograph of section from antrum membrane removed from a patient suffering from acute chorea. The patient recovered rapidly following the operation.

sense of tightening in the throat, accompanied by wheezing. A dose of .001 cc. did not produce such an effect, and the patient is continuing to use this dosage, administered once a week. Her asthma has again entirely ceased.

*Group 2. Chronic Septic Arthritis.* A number of arthritis patients have sinus infections as causative or associated factors. Some of them have received such prompt relief of joint symptoms following removal of these infected tissues that no reasonable doubt existed as to the etiologic rela-

tionship. In others the sinus infection seemed to be but one of several focal infections.

*Case 1.* IRC, age 44, November, 1927. The patient has suffered chronic back pain referred into right and left sciatic regions for one year, confining him to bed most of the time. Examination showed a spinal arthritis with considerable lipping in the lower thoracic spine, partial bridging between the 10th and 11th vertebrae, and some proliferative changes about the 3rd, 4th and 5th lumbar vertebrae. Chronic non-purulent hyperplastic double antrum disease was found, and a double radical antrum opera-

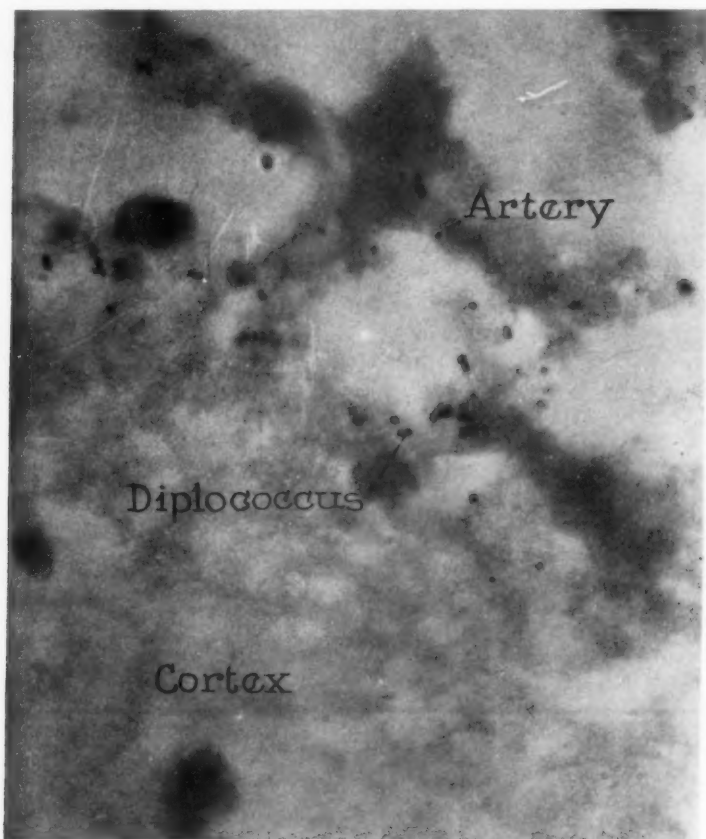


FIG. 11. Microphotograph of section of cortex of rabbit's brain inoculated intracerebrally with 0.2 cc. mixed dextrose-brain broth culture of antrum membrane removed from patient No. 1—neurologic group. Many diplococci are seen in this section.



tion done December 3, 1927. A general thickening throughout both antrums existed; the membranes were edematous, fibrous and more tightly fixed to the bone than normal. Cultures from swabs and from the tissues from the right antrum showed a growth of hemolytic and green-producing streptococci. The left antrum swabs gave a growth of long chain, green-producing non-hemolytic streptococci and the tissues gave a growth of a few hemolytic colonies of streptococci

and a moderate number of green-producing streptococci. A rabbit inoculated with a combined mixture of the cultures showed arthritic lesions in both hind limbs, but cultures from these joints remained negative. (The joint fluid alone was cultured.)

Rapid improvement of the patient occurred following the operation, and he now reports himself practically free from pain and that he is able to carry on his farm work without difficulty.

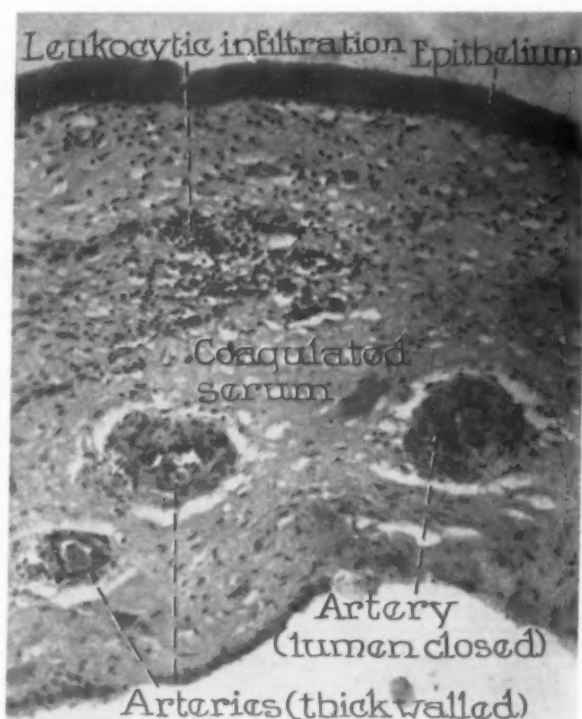


FIG. 12

FIGS. 12 to 17 inclusive. Microphotographs of sections of antrum membranes removed from patient No. 2—chronic atherosclerosis group. Note extensive fibrosis and thrombosis of blood vessels. Diplococci are shown on the surface of the mucous membrane, in the submucosa, within the wall of an arteriole, and in the coagulum of an arteriole's lumen.

NOTE: The tissues are stained according to Lillie's modification of the Gram Stain (Lillie, R. D., The Gram Stain, Arch. of Pathol. 5:828-834, 28). Precaution is taken to prevent artifacts. The tissues are fixed immediately in formalin as they are removed in the surgery. After paraffin impregnation sections are cut 5 micra in thickness. These are mounted on clean slides using sterile water. The sections adhere to the slides without the intervention of any cementing substance, being brought into contact with the glass by the evaporation of the layer of water on which they are floated. The materials are covered to prevent air borne particles from falling on the sections, and the stains are freshly filtered.

*Case 2.* APW, age 39, January, 1929. The patient has been entirely crippled, unable to work, and, for the most part, confined to bed for the past six months, during which time he has lost 25 pounds in weight and much strength. Most of the joints of the body have been involved, particularly both elbows, left knee and foot, and right knee; both elbows having developed contractures. Infected teeth had been previously removed. Cultures from the prostate were negative. A chronic purulent and hyperplastic double antrum disease was present, and was radically removed January 12, 1929, the lining being definitely thickened, edematous, and each antrum containing free

pus. Cultures from the tissue of the left antrum gave a mild growth of green-producing streptococci and staphylococcus albus. Cultures of the right antrum tissue gave greenish streptococci, a few staphylococcus albus and a few micrococcus catarrhalis. The rabbit inoculated with mixed cultures, autopsied in 48 hours, showed no lesions.

The stools cultured gave non-hemolytic green-producing streptococci and a few colonies of non-hemolytic pleomorphic diplococci. The patient's blood serum showed a complement titer of 2. The complement fixation with the above strains were, first, with green streptococci, +3; second, with diplococci, +2. A sensitized vaccine filtrate

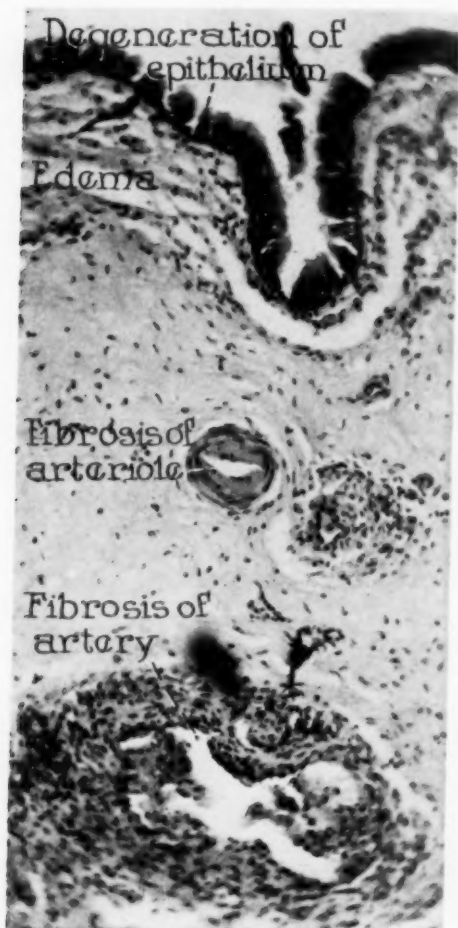


FIG. 13



FIG. 14

was prepared from these organisms. Seemingly this vaccine gave what we have looked upon as specific reactions and the use of the vaccine filtrate was continued at doses of .0002 of a cc., a point beneath that dosage which gave a negative phase reaction.

The left elbow and the right knee still remain somewhat swollen and somewhat tender, but the patient reports continued improvement. About a seventy-five per cent recovery has been made by this patient following the operation and the use of the vaccine.

*Case 3.* HS, age 49, March, 1928. For one year patient has suffered severely from chronic arthritis, affecting chiefly the back, ankles, right shoulder and hands, but with more or less pain over the entire body. All previously found foci of infection had been

removed. Examination of the sinuses gave only suggestive findings. The roentgen films both with and without lipiodol showed a thin lining membrane with the possibility of a cyst-like defect in the right antrum. An exploratory examination of the sinuses alone was advised, to which the patient consented. The right antrum revealed a cystic abscess extending along the lateral wall. A moderate generalized thickening of the membranes of the right antrum was found. The left antrum contained some free mucopus and the lining membrane was generally thickened and edematous throughout. Cultures from both antra gave a growth of a short chain diplo-streptococcus which produced slight hemolysis and slight green coloration of the blood agar. The cultures injected intravenously into a rabbit caused death in 24 hours. There was resulting



FIG. 15

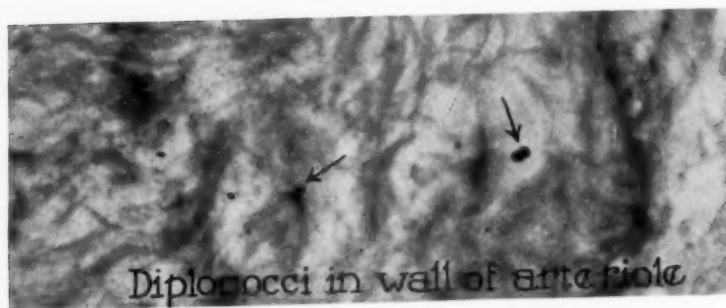


FIG. 16

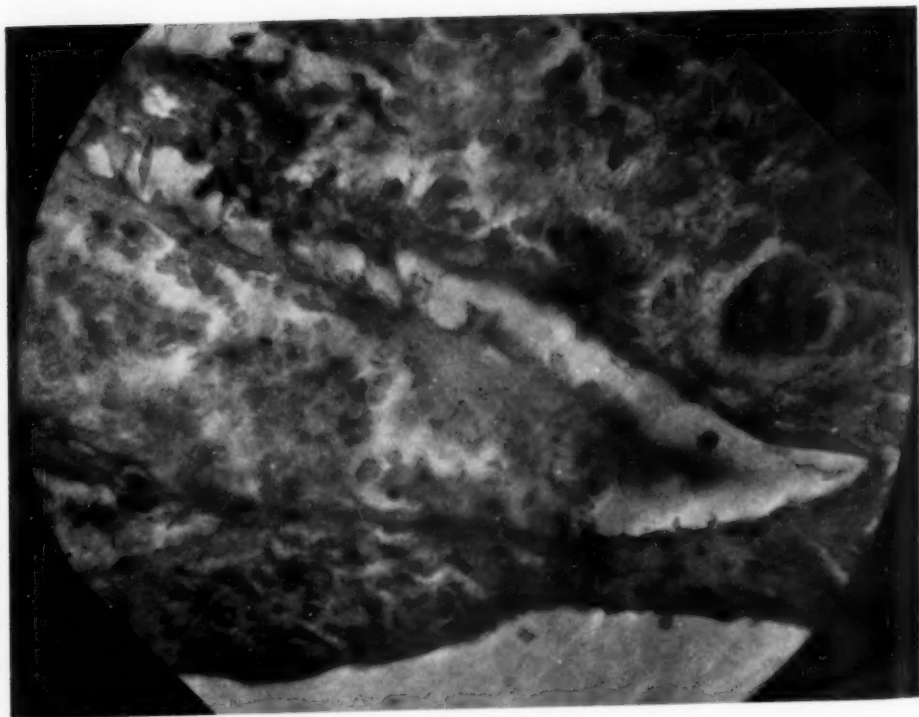


FIG. 17

involvement of many joints, and a slight enlargement of both kidneys. Cultures from the joints gave a growth in pure culture of slightly green producing streptococci.

Recovery from the arthritis was unusually prompt in this patient following the operation, and for two years he has been well.

**Group 3. Chronic Anemia.** Many patients suffering from chronic sinus disease have a moderate grade of secondary anemia which remains fixed until the infection is removed. Occasionally the anemia dominates the picture. The hemoglobin remains about 50 per cent and the red cells about 3 million in spite of all empiric methods of treatment. In a few cases of pernicious anemia the removal of an associated sinus disease has seemingly influenced symptomatic recovery.

*Case 1.* Mrs. FLW, age 48, October, 1927. The patient gives a history of gastrointestinal trouble for a year—pain, bloating, periodic constipation. She has had a pale color, and has been generally weak for a longer time. Examination revealed a chronic cholecystitis with complete non-filling of the gallbladder, and a secondary anemia of 50 per cent hemoglobin, 3 million red cells, and a seemingly normal differential count. No distinctive type of secondary anemia picture could be determined. There was present a chronic non-purulent hyperplastic double antrum disease.

It was found possible to relieve the gastrointestinal distress, due to the related motor disturbances, by means of a smooth diet, but the blood picture did not improve in response to therapy. Believing that the antrum disease was of more importance than the affected gallbladder, a double radical antrum operation was performed November 15, 1927, which showed the antra filled with polypoid hyperplastic tissue and thick mucus but no free pus. Cultures of the right antrum gave a growth of non-hemolytic green-producing short chain streptococci with a few colonies of hemolytic long chain streptococci. Cultures of the left antrum gave a growth of

non-hemolytic green-producing short chain streptococci.

Convalescence was prompt, and with the patient's convalescence a noticeable response in her blood picture was noted. She left Portland with a blood count of 89 per cent hemoglobin, 4.65 million red cells, and a color index of .95. Her blood picture has subsequently become normal and aside from occasional distress she remains well.

*Case 2.* Miss TR, age 48, December, 1928. The patient has suffered off and on for three years with sore tongue, loss of strength, marked paleness, irregular bowel, and attacks of pain under the right costal margin. The blood picture and general physical examination were very suggestive of pernicious anemia. But added to this picture was marked dental sepsis, a chronic cholecystitis, and chronic hyperplastic antrum disease. Relief of the gastrointestinal symptoms was obtained by diet regulation. The anemia was slow to respond to therapy, and because the sinusitis seemed to be definitely of importance, a double radical antrum operation was done January 8, 1929. There was generalized thickening of the lining membranes with edema. Swabs and cultures from the antra gave a few colonies of staphylococcus albus and a culture of green-producing streptococci.

The patient's general health improved rapidly after the removal of this pus infection. It had not responded to a previous removal of her dental infection. She has become stronger, her blood picture is within reasonably normal limits, though still showing characteristics of a pernicious type. She continues to eat glandular meats daily. We think this patient's general health and blood picture have been distinctly modified by the removal of her sinus sepsis.

**Group 4. Chronic Atherosclerosis.** A considerable number of patients with organic heart disease have an accompanying chronic sinus infection. Removal of the sinus infection in instances of rheumatic heart disease has not, in our experience, resulted in improvement of the patient's health. The

type of heart disease, however, spoken of by Benson<sup>2</sup> as atherosclerosis and by Clawson<sup>3</sup> as myocardial fibrosis, has been, in certain instances, remarkably bettered from a clinical standpoint by such treatment. The two patients noted herewith illustrate this point. Special note should be made of the extensive arterial fibrosis in the tissues removed from these sinuses (Figs. 12 and 13). These vessel changes have not thus far been seen in the sinus membranes removed from other patients. They suggest a selective action for the blood vessels on the part of the microorganisms present. These patients are especially apt to suffer coronary occlusion.

*Case 1.* GC, age 62, June, 1929. The patient has suffered shortness of breath for six years; has been easily exhausted for the past four years, and worse the past month. He has had a chronic cough, non-productive most of the time, but periodically has had head discharge. His blood pressure has been elevated for at least two years. Shortness of breath has been the most distressing symptom. One flight of stairs must be taken very slowly, and then is accompanied by dyspnea and heart palpitation. For the past three years he has been considered primarily a cardiac case, and his life has been modified to meet this condition. Undoubted cardiac pathology exists. Electrocardiograms would indicate a right bundle branch block. The arch is widened, but the right heart is 3 cm. and the left heart 9.8 cm., and the cardio-respiratory ratio is within 50 per cent. The absence of substernal dullness also points to the absence of failure. Because of the absence of cardiac failure, the possibility of his chronic sepsis being the primary

cause of his illness was considered. Lipiodol roentgen films showed a general uniform thickening in both antra. On June 24th a double radical antrum, and a trans-antral ethmo-sphenoidectomy on both sides was performed. There was definite hyperplasia of all of the lining membranes without free pus. Cultures of the right antrum gave a few colonies of staphylococcus aureus, a moderate growth of the staphylococcus albus, a few beta hemolytic streptococci, and a heavy growth of a green-producing streptococcus. The left tissue gave a moderate growth of staphylococcus aureus, a few staphylococcus albus, occasional micrococcus catarrhalis, occasional hemolytic streptococci, and a heavy growth of a green-producing streptococcus.

Symptomatic recovery was very prompt. On the 7th of October, 1929, he reported feeling well. He had no dyspnea, no suggestion of heart trouble. His blood pressure was 144-76. Three months later he again made the same report.

*Case 2.* RMW, age 59, May, 1927. The patient entered hospital with cardiac failure on the basis of the above cardiac pathology. Under hospital control it was found impossible to restore compensation. In the hope of obtaining compensation, it was decided to remove carefully all pus foci. June 1st tonsillectomy was performed and the patient had a stormy convalescence. The degree of his heart failure increased temporarily. On June 29th a double radical antrum operation was performed without much disturbance of the patient. Cultures from the left antrum gave a growth of slightly hemolytic streptococci and of non-hemolytic diplococci. Cultures from the right antrum gave a growth of non-hemolytic diplococci.

Following the removal of the infected tissue, compensation returned promptly and quite satisfactorily. For a year and a half he was in fairly good health. He returned to his business duties and also enjoyed fishing as a pastime. He died suddenly with a history of an acute coronary occlusion.

*Group 5.* General Malaise. Many patients having a chronic sinusitis complain chiefly of merely being tired.

<sup>2</sup>BENSON, ROBT. L. (The Present Status of Coronary Arterial Disease) Arch. Path. & Lab. Med., Vol. 2, Dec., 1926, pp. 876-916.

<sup>3</sup>CLAWSON, B. J. (Myocardium in Non-Infectious Myocardial Failure) Am. J. Med. Sci., Vol. CLXVIII, 5, Nov., 1924, p. 648.



Often different etiological factors are found in such patients that could produce a general malaise, but in a certain number of them the sinus infection has proved to be of great importance.

*Case 1.* Mrs. KH, age 54, September, 1929. This case illustrates a type of patient frequently encountered who complains for the most part of general malaise, weakness and nervousness, without the patient being of a general asthenic type of constitution, and with the presence of several etiological factors to consider. For ten years the patient has had attacks of pain in the stomach and right upper quadrant. She has been constipated, and has had much bloating and distress through the abdomen. For years she has had frequent head colds with considerable post-nasal drainage. For the past 2½ years she has been especially weak, tired, and nervous. Examination showed a chronic hyperplastic sinusitis, chronic cholecystitis with stones, a spastic type of colon constipation, and a moderate grade of secondary anemia.

Under control in the hospital it was found possible to regulate the bowel and relieve the motor disturbance at the end of the stomach incident to the gallbladder disease, but she did not feel especially better. It was therefore decided that the chronic sinusitis was of more importance than the gallbladder disease, and on September 24, 1929, a trans-antral ethmo-sphenoidectomy on both sides was performed. There was well marked hyperplasia of both antra, slight sphenoid and ethmoid thickening. Cultures from the antra showed, from the left, gram positive alpha hemolytic streptococci, and a few colonies of staphylococcus albus; from the right a few colonies of alpha hemolytic streptococci, a few colonies of staphylococcus albus and a few colonies of micrococcus catarrhalis.

A general improvement in the patient's health took place quite promptly following the operation, and the regulation of the bowel by means of a smooth diet continues to give her relief from the gastrointestinal distress.

*Group 6. Neurologic Group.* An infectious cause for the so-called motility disorders, spasmodic tic, torticollis, chorea, epidemic hiccup, periodic hyperpnea, has gained credence in the last few years. The work of Rosenow has been of special importance in this field. Whether these disorders will ultimately be linked with encephalitis lethargica remains as yet problematical, but there are many suggestive facts being noted, which suggest a close relationship, as individual cases are being more closely studied. The following three cases of tic, for instance, may well be removed from a psychogenic origin and be given an infectious cause. In the entire group of cases listed herewith the seemingly important micro-organism found in culture has been a pleomorphic non-hemolytic faintly green-producing streptococcus which, nearly always in brain tissue and often in the tissues removed from the sinuses, seemingly exists as a diplococcus. These clinical cases which have been, without reasonable doubt, linked with the associated sinus disease—offer to the problem of encephalitis lethargica at least the suggestion of a new approach for study.

*Case 1.* DB, age 9, December, 1929—Chorea. The child developed a mild chorea about a week ago that has extended to the loss of control of the right hand and arm and the right leg and foot. Aside from restlessness he is otherwise quite well. In 1927 his tonsils were removed. A month ago he had a head cold with fever and much post-nasal drainage. He has had more or less discharge from his head for a long time. A question of diplopia arose in September while the child was in school. He complained of seeing double from time to time. Examination revealed a soft systolic mitral murmur without evidence of cardiac failure,

and general thickening of both right and left antrums with polyp formation. Double radical antrum operation performed on December 10th, removed a thickened polypoid membrane from the left antrum, which also contained free pus, and a moderately thickened membrane from the right antrum.

Cultures from the tissues showed many colonies of alpha hemolytic streptococci, a few colonies of gram positive slightly hemolytic diplococci, and a few colonies of beta hemolytic streptococci, and of staphylococcus albus. A rabbit inoculated intracranially began to show, in 24 hours, definite choreiform movements. It was unable to walk, and seemed particularly unable to control its right side. Slight irritation of any part of its body produced a definite spasm. It died in 36 hours. Autopsy showed increased fluid in the knees, wrists, right hip and right elbow joints; there were inflammatory changes in the heart and the brain showed definite encephalitis. Cultures from these organs gave numerous colonies of alpha hemolytic streptococci, a few of beta hemolytic streptococci, and a few of a gram positive diplococcus. Grossly the brain and meninges were edematous; the cerebral vessels engorged with blood, the substance of the brain soft and friable, but there was no purulent exudate. Microscopic sections revealed edema and hyperemia. The meninges were thickened and contained enlarged endothelial cells, with occasional polymorphonuclear leukocytes and spindle cells in the tissue spaces. Some areas of the cortex were soft and necrotic. There was no evidence of leukocytes within the brain tissue. The Lillie modification of the gram stain showed gram positive diplococci in the areas of cortical softening and in the perivascular tissues of the meninges. The heart and kidney showed parenchymatous degeneration. In another rabbit injected intravenously, the brain was edematous and hyperemic, but the tissue was firm; there was no evidence of softening, and bacteria were not found in the brain tissue; the cultures of the brain remained negative.

The boy is still in bed because of his endocarditis. All choreiform movements ceased soon after operation.

\*Case 2. PS, boy age 14, August, 1928—Tic. The first appearance of the child's tic followed a prolonged sinus infection at the age of 6. From that time until his sinus operation September 12, 1928, there had been many recurrent sinus infections, always followed by exacerbation of the tic. Lessening of the intensity of the infection was correspondingly accompanied by an improvement in the patient's general physical condition and a lessening of the severity of the tic. Some months before his operation he had a subacute flare up of the sinus infection that was accompanied by a severe return of the muscle spasms. His early sinus infections were purulent. During the final flare up no pus was seen, and the radiographs were indefinite, showing only a suspicion of thickening. Three antrum punctures, at weekly intervals, gave no macroscopic pus, but polymorphonuclear cells were always seen in the cytologic examination. A double radical antrum operation was done. This revealed a soft, uniform thickening of the linings without surface discharge.

Recovery has been very gratifying. The whole physical and mental development of the boy has improved markedly, and now he has but an occasional twitch of any of the previously involved muscles. He appears to be quite a normal boy.

Swabs and tissues from the right antrum gave a growth of staphylococcus albus and green-producing short chain streptococcus. Cultures from the left antrum gave a growth of staphylococcus albus, micrococcus catarrhalis, and a green-producing streptococcus.

Case 3. ER, boy age 14, November, 1928—Tic. Multiple tics began with acute onset without apparent cause six months before examination. Infected tonsils and purulent antral and ethmoid infection were determined. The tonsils and adenoids were removed with no improvement following. Double radical antrum operation was performed December 17, 1928. Definite thick-

\*Cases 2, 3 and 4 were studied by our associate Dr. Selling, and have been reported in detail (Arch. Neurol. & Psych.) Dec., 1929, Vol. 22, pp. 1163-1171.

ening of the lining membrane with polypoid edema and some fibrosis was found.

Following the antrum operation there was a reduction in frequency and intensity of the movements, but at the end of two months, the improvement not having been satisfactory, exenteration of the ethmoids and sphenoid sinuses was done. The lining of these cells was hyperplastic throughout. Following this last procedure there has been a steady improvement. There are slight residual tic movements remaining, but the boy is almost normal.

*Case 4.* HS, boy age 11, October, 1928—Tic. Multiple tics began gradually between the age of six and eight years, and became so pronounced at the age of ten that it was difficult for the boy to remain in school because of his jerking, twitching, and explosive speech. In his eleventh year he had violent attacks during which he became uncontrollable. Tonsillectomy had been previously performed without results. Radiographic evidence of chronic antrum disease justified exploration of the antra. The right antrum showed a moderate thickening and edema, and the lining contained three cysts. The left antrum showed definite hyperplasia in the alveolar recess. The rest of the lining showed very little change.

Very striking improvement followed the operation, but there continued to be periodic and at times severe recurrences of his tic for a period of three months. Since then, however, they have practically disappeared and the boy is considered quite normal at the present time.

Cultures from the left antrum contained a staphylococcus albus and micrococcus catarrhalis. Cultures from the right antrum gave a green-producing streptococcus.

*Case 5.* Mrs. HWQ, age 36, April, 1929—Tic. Periodically recurring muscular twitchings, involving the legs, the arms, the neck and the head, began five years ago. During the early years the right side of the body was more affected than the left, but for the past two years the muscle spasms have been more severe on the left side. Septic tonsils were removed three years ago, without influence. Many devitalized, abscessed teeth have also been removed from

time to time without influence. The patient has had very little if any post-nasal drainage. Examination of the sinuses showed very little if any thickening of the right antrum membrane. The left antrum showed thickening with multiple polypi. A double radical antrum operation, and a trans-antral ethmo-sphenoidectomy on the left side was performed May 18, 1929. A large cystic abscess in the left alveolar recess was found. The remainder of the antrum mucosa on both sides appeared to be thin. The left ethmoid and sphenoid membranes were also not appreciably thickened.

Swabs and cultures from the right and left antrum gave in cultures staphylococcus albus, green-producing streptococci and micrococcus catarrhalis. A rabbit inoculated with cultures of the tissues intravenously showed lesions in both hind joints and an irido-cyclitis of the left eye with conjunctivitis. Cultures of the heart's blood and of the anterior chamber of the eye gave green-producing streptococci. A second rabbit inoculated intracranially with .2 cc. of the cultures of the tissues died in 48 hours. The brain was hyperemic with exudate and severe hemorrhage areas. Cultures of the brain gave a growth of green-producing streptococci. This rabbit developed definite muscular spasm to the left, as shown by the moving picture film. Microscopic examination of the brain of rabbit #2 showed a round cell infiltration of the meninges, noted in dense formation about the blood vessels that dip down into the brain substance. Some polymorphonuclear leukocytes and eosinophiles were present.

The patient's subsequent history has been most instructive. There was a complete subsidence of the tic during the period of surgical convalescence, that is, for a period of two or three weeks. During this time a vaccine prepared from the cultures obtained from the brain of rabbit #2 was given to the patient to see whether there would be any reaction from its use. The dosage was stepped up and finally a dose of .5 cc. produced a very slight reaction. But following the reaction the tic began to return slowly but progressively with increasing severity. After two weeks the spasms ceased and the patient returned to her home. As they re-

appeared again the vaccine was started in doses of .0001 cc. By mistake the doses were increased in amount, and the spasms returned with great violence, completely invaliding the patient. After these violent muscle spasms subsided, a dosage of .000001 cc. was given, an amount which we found did not produce a negative phase reaction.

For the past four months the patient has continued to take this dose of vaccine once a week, and had become nearly free from all manifestations of the tic for two months; but recently slight negative phase reactions returned and the dosage has again been reduced to a point where no reaction occurs. The patient remains in good health.

*Case 6.* PA, age 27, logger, January, 1929—Torticollis and Tic. The patient was thrown, fifteen months ago while at work in the woods, and fell upon his back. At the time he did not seem to be bothered much and continued to work for two weeks. His head began then to draw spasmodically backwards to the right, the chin pointing to the left and upwards, and he suffered much pain. Spasms recurred at intervals of one-half to two or three minutes. In this condition he was examined by Dr. Selling, on the above date. His case was considered that of an organic torticollis, believing that in all probability there was a deep lying central lesion of a traumatic nature. At the same time a search for infections was made, with the result that infection of both antra was recognized. The possibility of the trauma having lowered the resistance of the brain structure so that this infection, (which before had been latent) could have produced focal brain lesions, was considered. The situation was explained to the patient, and, merely as a long chance, a double radical antrum operation, and a trans-antral ethmo-sphenoidectomy on both sides was performed. There was much polypoid thickening of the alveolar recess of the right antrum, and moderate edematous changes in the left antrum. Both anterior ethmoid and sphenoid linings showed but a moderate thickening.

Very gratifying results followed the operation. In May, 1929, the backward pulling of the neck was very slight. He had

been at work. He can hold his head down and move it from side to side, but there is still some tendency for it to turn to the right. Later reports have indicated a very good end result.

Swabs and tissues from both antra in culture gave a growth of green-producing streptococci and a few staphylococcus albus. A rabbit injected intracranially with .2 cc. of the tissue cultures, showed after 48 hours, tremors of the head, which was held backwards. It could move its forelegs but could not stand on them, and at times sprawled on all four legs. Autopsy showed a profuse hemorrhage and hyperemia of the brain and meninges. Cultures of the brain gave a greenish producing streptococcus.

*Case 7.* Mrs. FFW, age 51, January, 1927—Periodic Hyperpnoea. Periodic spells of distinct hyperpnoea, often accompanied with syncope, began 25 years ago. For several years the patient had repeated attacks. A second pregnancy did not influence the spells. The attacks came in very irregular intervals, day or night, but the patient always awakened at night during the early part of the period of hyperpnea. The attacks later subsided in frequency and severity until about six months ago when they became again very severe and very frequent. Complete neurological examination gave no important findings. Examination of the nose and throat showed an extensive atrophic rhinitis present on both sides, with almost complete loss of the inferior and middle turbinates. There was much discharge and crusting in the nose and pharynx.

Cultures from the washings of the antra in brain broth media gave a growth of a gram positive diplo-streptococcus. .4 cc. of this culture was injected intracranially into a rabbit which died 24 hours later. Autopsy showed hemorrhagic areas in the brain and softening in the medulla. Cultures from the medulla contained a non-hemolytic gram positive diplococcus. A similar organism was obtained from one hind joint, which showed a slight increase in the amount of fluid. Several devitalized abscessed teeth were removed and cultures showed a non-hemolytic green-producing streptococcus with a few diplococci. A rabbit inoculated intra-

venously with 4 cc. of this culture at autopsy revealed a joint lesion in the front leg from which a non-hemolytic streptococcus was recovered. The brain cultures were negative.

Because of the extensive atrophy, the patient was directed to douche the nose daily and use a lubricant. There was no operative work performed, although the margins of both antra were markedly thickened in the roentgen films.

The use of a vaccine prepared from the brain cultures in a dosage of .01 cc. was used weekly until the following September, without recurrence of any attacks. In December, following what the patient thought was an acute food upset, she had three more attacks, two light ones and one severe one. She again resumed the use of the vaccine for a time. She has used none for the past 14 months. She continues the daily douching of her nose and at present remains well.

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We gratefully acknowledge our indebtedness to the members of the department of pathology for their assistance in this work; especially to Mr. Herman Semenov—Fellow in Pathology—for the histological preparations and his constant help in many ways.



## The Relation of Changes in the Portal Circulation to Splenomegaly of the Banti's Type\*

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THE RELATION OF CHANGES IN THE  
PORTAL CIRCULATION TO SPLENO-  
MEGALY OF THE BANTI'S TYPE

**D**EFINITION of Banti's Disease: Splenomegaly of no obvious etiology is occasionally seen and has been frequently reported in the literature. The fact that it is usually accompanied by an anemia has given the condition the name of splenic anaemia. Banti<sup>1</sup> in 1894 described a series of cases characterized not only by splenomegaly and anemia with gastric hemorrhages, but also with a terminal cirrhosis of liver. This represented to him both a clinical and a pathological entity. The clinical picture was that of a young person presenting first a splenomegaly followed by secondary anemia, gastric hemorrhages, gastro-intestinal disturbances, and later the clinical picture of cirrhosis. Leukopenia has been described but even in Banti's original four cases it was not a uniform feature. The liver presented the picture of portal cirrhosis. The spleen was greatly enlarged but retained its general outlines. Its capsule was thickened

and often showed numerous dense adhesions to stomach and diaphragm. The splenic vein was tortuous and showed a chronic endophlebitis. Microscopically there was proliferation of the reticulum of the pulp and of the adventitia of the arteries of the Malpighian bodies, atrophy of the pulp, and subcapsular fibrosis. Banti believed the condition to be a primary splenomegaly with secondary blood and hepatic changes. He insisted upon the idiopathic nature of the disease, a stand which, of course, automatically dooms it as an entity to ultimate oblivion. He believed splenic anemia to be merely the first stage of the disease and that cirrhosis invariably followed if the patient survived. The contention was discredited at first by many, notably Rolleston<sup>2</sup>, who maintained that many cases of splenic anemia never developed cirrhosis. But it has since been generally conceded that the two conditions are fundamentally the same. The microscopic appearance of the splenic sinuses has been the subject of some dispute. Chiari<sup>3</sup> believed the pulp changes those of ordinary fibrosis rather than a specific reticulo-endothelial response. Banti himself did not believe the sinuses to be dilated but the majority of subsequent observers make

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that a part of the picture. Leon-Kindberg<sup>4</sup> agreed with Banti and thought that those splenomegalies with dilated sinuses were the result of obstruction of the splenic vein. The probable truth is that sinus dilatation may or may not be present depending on the age of the patient, and the speed of onset and duration of the fundamental etiologic factor which we shall attempt to indicate.

*The Primary Site of Disease:* It has been assumed for the following reasons that the spleen is of necessity the primary site of the disease; (1) The splenomegaly is often the first clinical phenomena, while clinical signs of cirrhosis appear late; (2) the left side of the liver, that receiving most of the blood from the spleen, sometimes shows most of the cirrhosis; and (3) splenectomy frequently cures or benefits these patients. Rebuttal can reasonably be made to all of these. (a) Even though an enlarged spleen appear first, it may readily be the result of an as yet unrecognized cirrhosis which will later show its more usual clinical picture. As will be pointed out subsequently, the amount of narrowing of the hepatic vessels in cirrhosis cannot be judged by the amount of fibrosis present, so that even by direct observation of the liver at the time of splenectomy one is unable to judge how much or how little portal obstruction is already present. (b) The left lobe of the liver is occasionally more involved than the right, as Séregé<sup>5</sup> points out, but he admits that blood to the left lobe comes not only from spleen but also from stomach so that there is no more reason to postulate a

toxin of splenic origin as the cause of the cirrhosis than one of gastric origin. As a matter of fact a cirrhosis of general distribution is much more often associated with the Banti's syndrome than one limited chiefly to the left side, so that the second reason finds little support. (c) The beneficial effect of splenectomy has been the most persuasive argument in favor of the splenic origin of the disease and yet this too is subject to serious question. As Mayo<sup>6</sup> has pointed out, splenectomy removes about 30% of the portal circulation so that a cirrhotic liver, unable to carry on the full circulation, may be able to maintain the remaining 70%, and when placed thereby at physiologic rest, may even recover some of its reserve power. In practical support of this the same author cites cases with well developed cirrhotic phenomena, without the Banti's syndrome, which, contrary to Umber's<sup>7</sup> contention, did show a marked improvement after splenectomy. It can be seen therefore that all the arguments for primary splenic disease are far from reliable.

*Etiology:* Disregarding Banti's assertion that his "disease" must be without cause, one must consider a number of etiologic factors, the more important of which are infection, intoxication, and mechanical disturbance of the portal or venous circulations.

An *infection* or *infestation* of the spleen has been suspected by many authors as the cause of the condition. Numerous organisms have been advocated. Krumbhaar<sup>8</sup> quotes Gibson as having isolated a streptothrix; Yates, a diphtheroid, and Hollins a colon bacillus. Leon-Kindberg<sup>4</sup> felt that the

lesions resembled those of a plasmodian infestation. Gregoire et al<sup>9</sup> reported a case in which the spleen was loaded with mycelial threads and spores. The organism of malaria has also been proposed and the possible syphilitic nature of the disease has been repeatedly indicated. The very variety of these supposedly etiologic agents suggests at once that none is the true cause.

*Metabolic and infectious toxins* have been given the causative role in the symptom complex, not only for the splenic enlargement but the same or a secondary toxin developed in spleen has been supposed to give rise to the cirrhosis. That hepatic cirrhosis is on a toxic basis may be true but this does not enter the scope of this paper. The claims for intoxication as the cause of the original splenomegaly are so vague and indefinite that we feel they can be definitely disregarded.

*Mechanical Interference* with the portal circulation or splenic venous flow is probably the most important factor. Many observations demonstrate the fact that the whole picture of "Banti's disease," aside from the cirrhosis, may be produced by a variety of gross mechanical lesions of the portal system. The more striking of these are (a) thrombosis of splenic or portal veins, (Klemperer<sup>10</sup>, Rosenthal<sup>11</sup>, Goldmann<sup>12</sup>, Warthin<sup>18</sup>, Mallory<sup>13</sup>); (b) stenosis of splenic vein (Leon-Kindberg<sup>4</sup> from Nancrede); (c) obstruction from pressure from without—gall-stone impacted in common duct (Armstrong<sup>14</sup> from Mayo, W.); and (d) congenital narrowing of portal bed in liver with patent umbilical

vein and portal vein hypertension (Moschovitz<sup>15</sup>—four cases from the literature). Cirrhosis of liver, portal of biliary has been suggested by many as the cause of the portal obstruction (Rolleston<sup>2</sup> from Naunyn, Gilbert and Lereboullet<sup>16</sup>, Dürer<sup>17</sup>, Klemperer<sup>10</sup>).

Warthin<sup>18</sup> tried the effect of ligation of the splenic vein in dogs and rabbits. He observed a moderate splenic enlargement followed in a number of weeks by atrophy. Such sudden cessation of flow in the splenic vein is not comparable to the slower occlusions of disease. One might draw an analogy. Ligation of a ureter gives rise to slight hydronephrosis followed by renal atrophy. But if the occlusion is slow, partial, or intermittent great degrees of hydronephrosis develop. Warthin himself recognized that his experimental results were misleading and concluded in spite of them that portal or splenic vein obstruction does produce the splenic lesions of "Banti's disease."

*Cirrhosis as a Cause:* Most of the above mentioned lesions produce portal obstruction in a more or less obvious fashion but the vascular changes in liver associated with cirrhosis need further consideration. It is apparent to anyone who has studied sections of frankly cirrhotic livers that there is indeed a reduction in size of the portal vessels throughout and that if the same volume of blood is to pass through the liver as through a normal one it must do so under a greater pressure. But even in a liver without patent scarring recognized as cirrhosis one may have definite narrowing of the vascular bed. Attention was called to this by Gilbert and Lereboullet<sup>16</sup> who demonstrated,

in cases of splenomegaly with little or even no gross evidence of cirrhosis a productive, fibroblastic reaction about the fine biliary passages with compression not only of the duct lumen but also of the adjacent vessels of the portal sheath, especially the venule. They believed these to be evidence of unrecognized biliary tract infection and were able in some of their patients to obtain a history of previous temporary illness with jaundice.

Anatomically, of course, interference with splenic circulation by changes in the liver is possible since the portal and splenic veins are entirely devoid of valves. The lesions in spleen look like the result of long standing passive congestion; the development of collateral circulation with esophageal varices, gastric hemorrhage and early ascites are also signs of portal obstruction. The secondary anemia is usually the result of gastric hemorrhage, gross or occult, but even without the latter a similar anemia is found in pure cirrhosis and in splenomegalies the result of gross portal obstruction.

*Purpose of Present Study:* With this background in mind it is the purpose of the remaining part of this paper to report an attempt to measure, in a group of normals, a group diagnosed portal cirrhosis, and a group diagnosed "Banti's disease," the relative size of the hepatic portal radicals. The points to be studied were (a) the approximate quantitative narrowing of the vessels in cirrhosis and in "Banti's disease"; and (b) the relation of the degree of narrowing to the size of the spleen, the age of the patient, and the degree of cirrhosis.

*Material and Methods:* The material for study consisted of the routine liver sections of autopsies from the files of two large general hospitals, over approximately a 20-year period. Ten normals were selected from young individuals (15 to 30 years) who had died of acute infections. In doing this it was realized that the toxic changes in spleen make the weight of this organ of no significance to this study, but the establishment of a normal for portal vessels was all that was desired. Comparative studies of age and splenic weight were carried out only in the cases of cirrhosis and "Banti's disease." 23 cases in which the principal diagnosis of portal cirrhosis had been made and 4 cases diagnosed "Banti's disease" were used. A fifth case called "Banti's disease" showed great quantities of hemosiderin in liver and spleen. This case was omitted from the study because the effect of possible extraneous toxic factors on the organs (perhaps chronic copper poisoning) could not be excluded. The fact that most authors describe "Banti's disease" as occurring without pigmentation eliminates the case in the eyes of the majority.

Camera lucida tracings of the lumina of veins of the terminal portal sheaths were made, together with those of the immediately accompanying hepatic arterioles. The tissue was approximately from the same liver areas, namely just beneath the capsule, as is routinely taken in autopsy blocks. The cases were measured without knowledge of the diagnosis at the time of observation. The same microscope and camera lucida, with a constant tube length, side arm length, and mir-

ror angle were used, and all the tracings were made by the same individual. Actual calculation of the magnification was therefore unnecessary since all of them were on the same scale. A high power objective was used. In the normals there was no difficulty, but in the cirrhotic livers many vessels of the same type were found in the same mass of connective tissue, probably representing the remains of several collapsed lobules. For this reason careful selection was necessary to be sure that only the arteriole belonging to the venule chosen was traced. Occasionally in both normal and abnormal livers the portal radical was accompanied directly by two or rarely three arterioles. When this was absolutely certain the sum of the arteriolar measurements was used. The large number of small vessels of no particular structure, which represent the remains of liver sinusoids or new formed capillaries in the chronic inflammatory tissue, were avoided. Moreover only vein and artery in practical cross section or in almost exactly the same degree of oblique section could be utilized in order to obtain comparable figures. This again limited the number of observations possible on the two to five routine liver sections available in each case. Broken parts of the sections and branching vessels also could not be used. The number of suitable pairs of vessels for each case varied from 3 to 12, averaging about 6. On the normals a total of 59 tracings were made; on the cirrhosis 139; and on the Banti's 26. It was decided because of a degree of infolding present in many of the veins and some of the arteries, to measure the circumference of the

tracing of the vessel lumen rather than its diameter, although the work of Gilbert and Lereboullet<sup>10</sup> indicates that all of this infolding may not be artefact. Since absolute cross section was not possible the size of the vein was estimated in relation to the size of the artery rather than making a direct comparison of the size of the veins themselves. Thus the measurements represent an estimate of the relative size of the arterial and portal blood vascular beds in the liver.

It will be easily seen that many errors must necessarily be present in such a study but these have been reduced to the minimum by careful selection, the use of proportionate rather than absolute sizes, and the fact that such errors are more or less constant ones throughout. The average ratio in each case of arterial lumen circumference to vein lumen circumference (Ha-Pv ratio) was calculated and recorded and the average of this ratio was put down for each group, as seen in the tables. In addition there was noted the number of observations, age of the patient, weight of the spleen and an estimate of the amount of microscopic fibrosis in the liver. The weights were reported in grams. The tracing measurements were made in inches, but of course measurements by any other scale would give figures of exactly the same relative value.

The cases were grouped as follows: Table I, normals; Tables II and III, cases with the primary diagnosis of portal cirrhosis; and Table IV those definitely called "Banti's disease." The cirrhotoses have been divided, more or less arbitrarily, into two groups, those without obvious splenomegaly, (Table

II, spleens less than 300 gms.) and those with definite splenomegaly (Table III, spleens from 300 to 805 gms.). The latter group forms an intermediate one between those in which cirrhosis dominates the picture and those in which the splenomegaly is the prominent feature. The cases have been arranged in each table according to the weight of the spleen.

### RESULTS

(1) *Spleen*: Examination of spleens of the intermediate group showed in varying degrees the picture described by Banti. There were some with perisplenic adhesions, all showed fibrosis, most of them had sclerosis of the adventitia of the Malphigian vessels, and many showed engorgement and sinus dilatation. A number of them showed capsular thickening and sub-capsular fibrosis. The spleens in the cases of frank cirrhosis often showed fibrotic changes. The spleens of the "Banti's disease" group showed the histologic

changes supposed to be characteristic of this condition.

(2) *Degree of Cirrhosis*: It is apparent from the tables that the degree of hepatic fibrosis bears relation neither to the size of spleen, age of patient nor to the hepatic artery-portal vein ratio. Whatever constricts or reduces the size of the portal venules is experimentally as well as theoretically not simply the compression of contracting scar, since as much or more reduction is noted in

TABLE I—NORMALS

Number	Observations	Age	Ha.-Pv. Ratio
(1) M-54-29	5	35	1-4.6
(2) M-47-29	5	30	1-3.4
(3) M-71-29	7	30	1-7.3
(4) M-72-29	5	28	1-7.9
(5) M-56-29	6	28	1-8.2
(6) M-70-29	7	24	1-5.4
(7) M-61-29	6	21	1-8.4
(8) M-75-29	5	20	1-4.5
(9) M-76-29	6	19	1-5.1
(10) M-51-29	7	15	1-6.2
Average of	59 obs.	25	1-6.0

TABLE II—CIRRHOSIS—SPLEEN LESS THAN 300 GMS.

Number	Obs.	Age	Degree Cirrhosis	Wt. of Spleen	Ha.-Pv. Ratio
(1) A-26-21	3	40	Moderate	275	1-5.2
(2) A-31-23	8	40	Mild	240	1-5.0
(3) A-19-29	6	47	Severe	220	1-5.8
(4) A-35-27	5	64	Mild	205	1-5.6
(5) M-40-25	5	72	Mild	175	1-3.9
(6) M-74-22	4	64	Severe	165	1-3.2
(7) A-7-28	5	64	Mild	155	1-5.4
(8) M-30-29	6	66	Severe	155	1-3.1
(9) M-33-23	4	55	Moderate	120	1-3.8
(10) A-6-28	7	65	Severe	100	1-2.5
(11) A-20-25	6	70	Severe	95	1-3.4
(12) M-9-27	5	65	Moderate	80	1-4.7
Average of	64 obs.	59		165	1-4.3

Approximate reduction of vascular capacity in liver 29%.



TABLE III—CIRRHOSIS—SPLEEN MORE THAN 300 GMS.

Number	Obs.	Age	Degree Cirrhosis	Wt. of Spleen	Ha.-Pv. Ratio
(1) M-12-30	11	45	Severe	805	1-2.3
(2) A-2-23	3	39	Moderate	645	1-4.3
(3) A-70-28	9	41	Severe	625	1-2.6
(4) M-63-28	4	33	Severe	600	1-4.4
(5) M-62-22	7	44	Severe	525	1-2.1
(6) M-43-29	7	46	Severe	380	1-2.8
(7) M-5-30	10	44	Mild	375	1-3.7
(8) A-13-28	5	73	Moderate	335	1-4.1
(9) A-24-29	8	52	Severe	330	1-4.0
(10) M-28-23	4	75	Moderate	300	1-3.3
(11) A-65-24	7	62	Mild	300	1-4.2
Average of	75 obs.	50		475	1-3.4

Approximate reduction of vascular capacity in liver 43.5%.

TABLE IV—CASES DIAGNOSED "BANTI'S DISEASE"

Number	Obs.	Age	Degree	Wt. of Spleen	Ha.-Pv. Ratio
(1) M-52-29	12	28	Severe	1300	1-2.8
(2) M-81-25	5	19	Mild	1000	1-2.4
(3) M-81-29	5	29	Severe	505	1-2.8
(4) M-11-22	4	46	Moderate	300	1-3.2
Average of	26 obs.	30		776	1-2.8

Approximate reduction of vascular capacity in liver 53%.

cases with little fibrosis as in those most extensively sclerosed. For instance it is seen that Case 2, Table IV, has an extremely large spleen and but little apparent evidence of cirrhosis. Yet the hepatic portal venules are greatly narrowed (ratio 1 to 2.8). Such a case might have been considered splenic anemia without cirrhosis and placed in the category of primary splenomegaly had not the measurements definitely indicated a vascular lesion in liver.

(3) *Age*: Age has apparently a definite effect on the amount of splenic enlargement. The average age in the

"Banti" group was 30 years, that of the intermediate group 50 years, and that of the cirrhotic group 59 years. If Tables II, III and IV were superimposed it would be apparent that, with a few exceptions, as age increased the amount of splenic enlargement decreased in all three groups. One can also see that the division into groups is an entirely artificial one, the one group overlapping and merging imperceptibly into the other in a continuous transition from frank cirrhosis through intermediate forms to the picture of "Banti's disease." Thus it looks as if the older the spleen the less able



it is to enlarge in response to back pressure and that perhaps the reason cirrhosis predominates in older individuals and splenomegaly in younger ones is simply that with the same degree of portal obstruction the young spleen enlarges to a much greater degree than the older one. Expressed mathematically then, the amount of splenic enlargement is roughly inversely proportionate to the age. Chart I shows the relationship graphically. The entire group has been arranged in order of age, and shows the rapid drop in splenic enlargement with increasing age. The effect is more marked in the earlier decades than in the later ones.

(4) *Narrowing of the Hepatic Vessels*: Inspection of the tables shows a normal Ha.-Vp. ratio of 1 to 6.0 (Table I). The cirrhotics with little or no splenomegaly (Table II) showed a ratio of 1 to 4.3, a drop of 29% in the capacity of the portal vessels. The intermediate group, i.e. cirrhosis with

splenomegaly had an average ratio of 1 to 3.4, or a 43.5% reduction. The group diagnosed "Banti's disease" averaged 1 to 2.8, representing a 53% loss of normal vascular capacity in the hepatic portal radicals. Attention is called to the great regularity of excessive vascular narrowing in the latter group regardless of the degree of hepatic fibrosis. Again, reference to the tables shows that just as was the case with age, throughout all the groups there is a gradual merging so that the Ha.-Vp. ratio of cases of the intermediate group fall in at one end with the frank cirrhosis and at the other end with those of "Banti's disease." It is also seen that the size of the spleen is in general directly proportionate to the degree of capacity loss and inversely proportionate to the degree of available vascular bed. Chart II shows graphically the relationship of the size of the portal venules (Ha.-Pv. ratio) to the weight of the spleen.

Chart I.

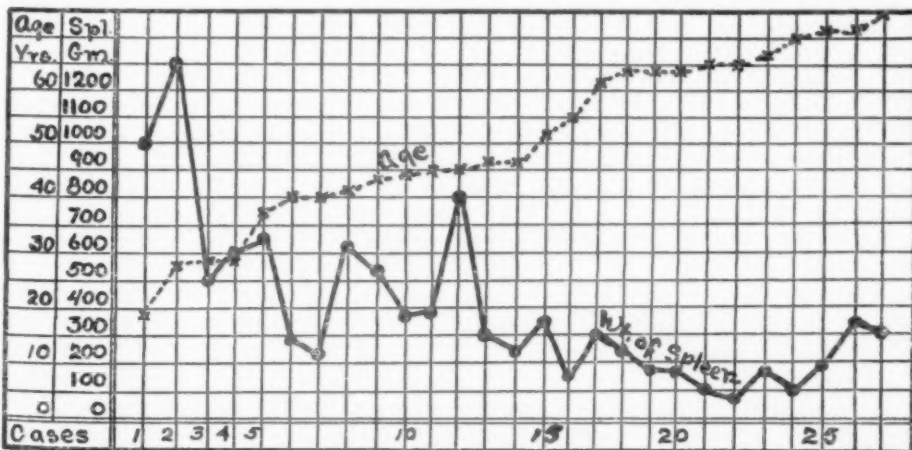


CHART I. Shows the 27 cases of Cirrhosis and "Banti's Disease" arranged according to age. Note the marked decrease in Splenic enlargement with advancing age.

It shows the great *increase* in splenic enlargement with decrease in vessel size. Apparently a certain degree of narrowing (approximately 50%) can be compensated, after which the effect is much more pronounced. The percentage losses cited above seem quite large but probably do not represent as much reduction as occurs, since it represents merely the reduction in relation to the size of the arterioles, many of which are undoubtedly atrophic, and does not take into account possible pressure infolding. It must be admitted that a certain number of small vessels are found in the sclerosed portal sheaths which may represent new

formed vessels associated with the fibroblastic reaction, but these are so small that their resistance must be great and the formation of extensive collateral circulation easily shows that these are far from able to compensate for the loss of normal vascular area.

(5) *Relation of Age to Size of Vessels in Liver*: Since the curves for age and Ha.-Vp. ratio are so similar it might be argued that the narrowing of vessels was simply the result of advancing age. Chart III, however, shows the relation of Ha.-Pv. ratio to age in the normals and in those cases of "Banti's disease" and cirrhosis falling in the *same age range*. It is readily

Chart II.

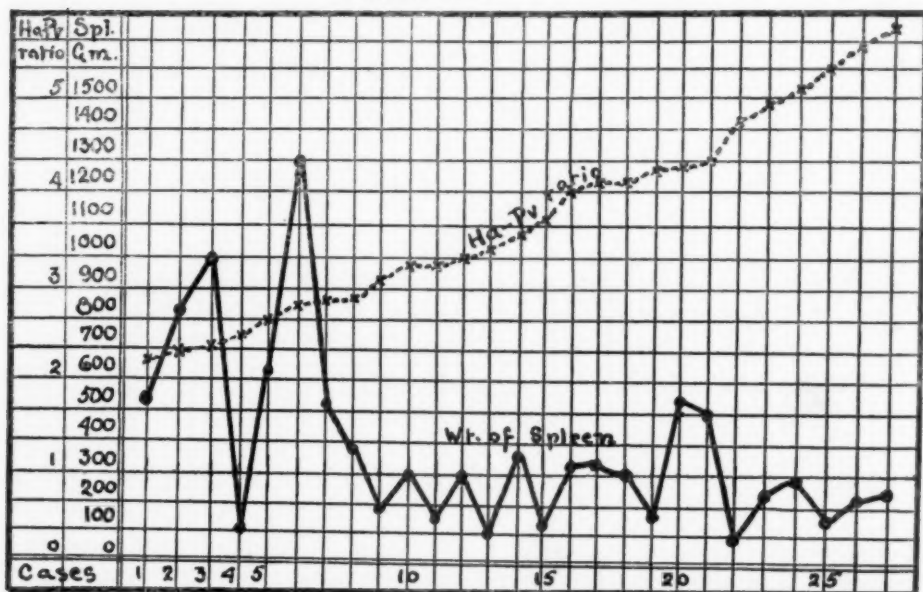


CHART II. Shows the 27 cases of Cirrhosis and "Banti's Disease" arranged according to the Ha-Pv ratio (ratio of circumference of hepatic arterioles to portal venules in the same portal sheaths). Note the marked splenic enlargement in the cases with greatly contracted portal venules (ratios of less than 1-3.0, i.e., half the normal ratio of 1-6.0). Case 4, an exception, was 65 years old and no doubt age was a strong factor in preventing splenic enlargement.

seen, even though the number is small, that the hepatic portal radicals are much smaller at the same age in the pathologic cases than in the normal ones.

#### SUMMARY AND CONCLUSIONS

In conclusion we may say that both from the observations cited in the literature and from our own results there is strong evidence that in those

conditions known as splenic anemia and "Banti's disease" we are dealing with mechanical alterations of the portal blood flow interfering with the free exit of blood from the spleen. The more important lesions bringing this about may be summarized as follows:

#### I. Congenital anomalies.

1. Patent umbilical vein with excessive portal flow.

Chart III.

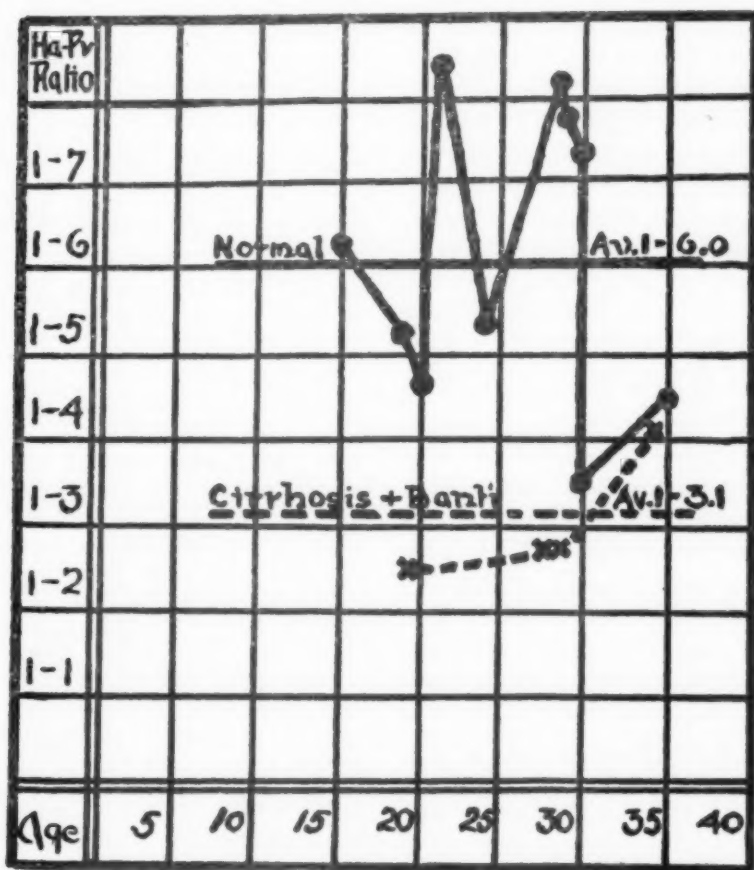


CHART III. Shows the relation of Ha-Pv ratio to age in the normals and in those cases of Cirrhosis and "Banti's Disease" which fell in the same age range. Note that the Ha-Pv ratio in the pathologic group falls far below the normals, so that vessel narrowing in liver is not merely a function of age.

2. Hypoplasia of liver or of portal veins in liver.
  3. Narrowings or distortions of lumina of vessels.
- II. Pressure from without on portal or splenic vein by calculus, tumor or adhesions.
  - III. Cirrhosis of liver.
  - IV. Thrombosis of portal or splenic vein.

It is obvious that these changes do not always produce a picture in which the splenomegaly predominates. Other factors are present. Probably the most important of these is age; the younger individuals responding with a greater degree of splenic enlargement than the older ones. In the cases associated with cirrhosis the factor of importance is not the fibrosis present *but the degree of vascular narrowing*, which as

we have seen can be extreme even when there is little if any gross fibrotic reaction and even when there is little microscopic scarring. We do not know what causes the vascular narrowing or even the cirrhosis. If toxic, it may come from the bowel or stomach as readily as from the spleen. One undoubtedly sees clinically the syndrome of "Banti's disease" but that this is a primary splenomegaly with secondary cirrhosis seems unfounded. The indications are that a number of pathological conditions, such as described, can give rise to this picture.

*Note:* Thanks is expressed to Dr. J. A. Perrone for assistance in translations, to Dr. S. R. Haythorn for the use of his sections and records, and to Dr. H. H. Permar for his valuable suggestions and assistance in preparing this paper.

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## The Association of Cholecystitis With Cardiac Affections—A Study Based on 109 Cases\*

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**I**NSTANCES in which infections of the gall bladder are complicated by affections of the heart are numerous and most physicians have had more or less experience with the association. It is well known that an existing cardiac affection may be greatly aggravated by a superimposed acute or chronic cholecystitis, and likewise the idea is gaining ground that a chronically diseased gall bladder may act as a focus of infection, initiating baneful changes upon organs and tissues unassociated with the gastrointestinal tract.

### LITERATURE

Tessier<sup>1</sup> in 1879 classified cardiac disturbances depending on gastro-hepatic diseases. Gueneau de Mussy<sup>2</sup> in 1878 stated that the cardiac murmur found in gall bladder disease was due to the paralyzing effect of bile salts upon the vasomotor and general circulatory system. Gangolphe<sup>3</sup> believed the principal effect upon the heart was on the papillary muscles, while Fabre<sup>4</sup> considered it a myocarditis due to the accumulation of bile salts in the blood.

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Leva<sup>5</sup> in 1892 reported from Eichorst's Clinic in Zurich, 2 cases of ulcerative endocarditis resulting from gall bladder disease. In 1893 Oddo<sup>6</sup> of Marseilles reported a case of pericarditis and arrhythmia, which developed two days after an attack of biliary colic. Riesman<sup>7</sup> in 1907 and again in 1911<sup>8</sup> reported cases in which during an attack of biliary colic there developed mitral systolic murmurs which were not present previously, and which disappeared after the subsidence of the pain. This he interpreted as due to temporary cardiac dilatation, due to strain and increased tension. Robert Babcock<sup>9</sup> in 1909 and also in 1919<sup>10</sup> reported cases in which the symptoms were mainly referable to the circulatory system. These cases after careful study proved to have coexisting cholecystitis and some were much improved after biliary tract surgery. Hoppe-Seyler<sup>11</sup>, Umber<sup>12</sup> and Külles<sup>13</sup> in individual articles in the German literature comment on the relation of cardiac arrhythmias to gall stone colic. Lichty<sup>14</sup> in 1915, stated that while in appendicitis the cardiac disturbance was functional, in gall bladder disease the heart is more seriously affected. Sir Humphry Rolleston<sup>15</sup> in 1920 con-



firmed this view. Ransohoff<sup>16</sup> in 1924 stated that the association of cholecystitis and myocarditis was so common as to demand serious attention. Strauss and Hamburger<sup>17</sup>, Mayo<sup>18</sup> and others cite cases of myocarditis and various types of cardiac arrhythmias which were relieved or improved after surgical treatment of the biliary tract.

In the past two decades, therefore, and particularly since the monumental work on focal infection by Rosenow<sup>19</sup> in 1914, the infected gall bladder has been accused of being the primary focus for pathologic changes in many other organs, including the heart.

The foregoing citations from the literature as well as the experience of numerous practitioners, while showing that there often is an association of the two diseases, do not, however, indicate how frequently the combination occurs. From a practical standpoint it is important to know in what percentage of cases of cholecystitis, one may also expect to find an affected myocardium. As far as we have been able to ascertain, only two such studies have heretofore been carried out, the first by Willis and Fitzpatrick<sup>20</sup> of Rochester, Minn., in 1925, and the second by Leech<sup>21</sup> of Boston within the past year. They analyzed 596 and 116 cases respectively. Inasmuch as both these series deal with patients who presumably sought surgical intervention, and who probably had the more serious types of cholecystitis—of the first series 34% of all the cardiacs were operated upon, and the entire group of the second series had operations—it should be expected that more representative information might be obtained from a group studied in a medical service,

where the type, duration and severity of the disease would likely be more varied.

#### PRESENT STUDY

Our studies are based on 109 unselected cases of cholecystitis which were treated consecutively in the medical wards of Mt. Sinai Hospital since 1924.

The diagnosis of cholecystitis was made on the history, clinical findings and laboratory data which included x-ray studies, such as flat plate of the gall bladder area, cholecystography, duodenal drainage, icterus index and the Van den Bergh test. Frequently, to rule out other conditions, urologic studies including pyelography; pelvic examinations; x-ray of the lumbar spine and sacro-iliac regions; and gastro-intestinal x-ray studies were made.

The criteria for establishing a diagnosis of heart disease, consisted of a history of circulatory disturbance such as dyspnea, cough and so on; the presence of cardiac abnormalities as revealed by careful physical examination; blood pressure readings, and as required, orthodiagrams and electrocardiographic tracings.

There were 93 females and 16 males. The youngest patient was 21 years and the oldest 75 years. Chart 1 indicates the age distribution according to decades. Whilst children above the age of 12 were admitted on the medical service, there were no cases of cholecystitis before the age of 20. The greatest number of cases in a single decade numbered 31, and occurred in the fifth decade. The fourth, fifth and sixth decades totaled 79 or 72% of all the cases. There were 15 cases in the



third decade, and the seventh and eighth decades together numbered 15 cases—25 or 22.9% of these cases were calculous and 84 or 77.1% were non-calculous.

#### ASSOCIATED DISEASES

Focal infection either in the form of diseased tonsils, chronic sinusitis, den-

tal caries, endocervicitis or mild prostatic disease occurred in 106 of the 109 cases. Table 1 lists the most frequent associated conditions. There were 69 patients (63%) with heart disease, 57 (52%) with obesity, 9 (8%) with diabetes, 7 (6%) with sacro-iliac disease, 5 (4%) with ureteral stricture and 3 cases with chronic pancreatitis.

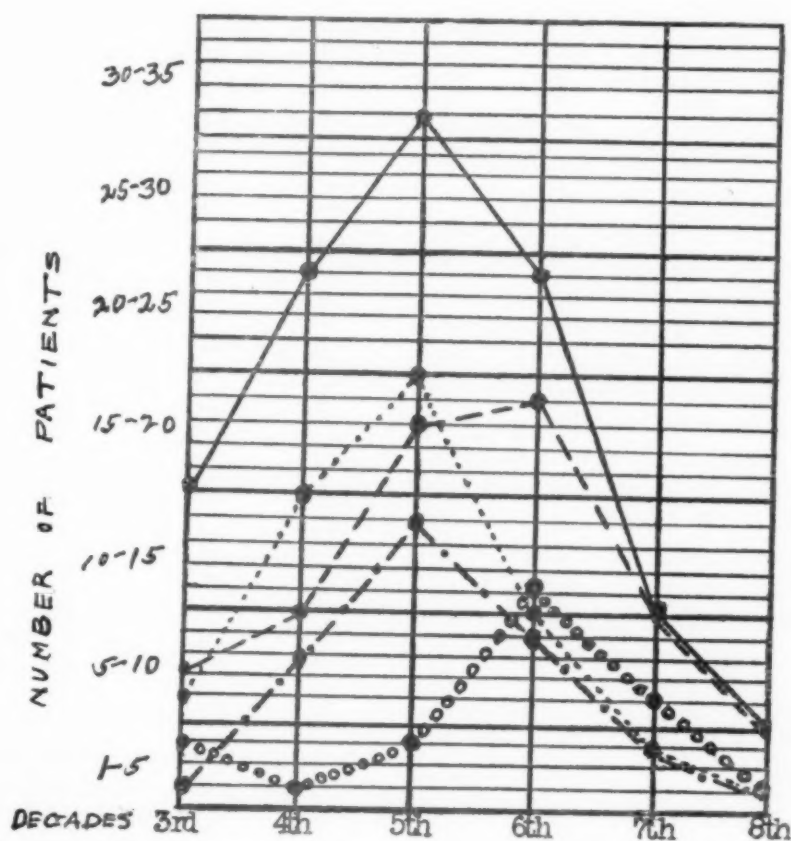


Chart 1. Showing the age in decades of 109 cases of cholecystitis; the number associated with obesity; the number associated with heart disease, comparing the fat with the lean.

- Cholecystitis.
- ..... Cholecystitis with obesity.
- Cholecystitis with heart disease.
- · — · — Cholecystitis with obesity and heart disease.
- o o o o o Cholecystitis with heart disease, no obesity.

TABLE 1.

Showing the number and variety of associated conditions in 109 cases of cholecystitis.

Heart Disease .....	69
Obesity .....	57
Diabetes .....	9
Sacro-iliac Disease .....	7
Ureteral Stricture .....	5
Pancreatitis With Questionable Malignancy .....	3
Chronic Appendicitis .....	3
Renal Calculus .....	3
Intercostal Neuralgia .....	3
Chronic Nephritis .....	3
Nephroptosis .....	3
Menopause .....	3
Spondylitis .....	2
Pelvic Inflammation .....	2
Miscellaneous .....	18

## HEART DISEASE

These totaled 69, and indicates that 63.3% of all the gall bladder cases had an associated cardiac condition. Chart 1 shows that the greatest number of heart cases occur in the fifth and sixth decades—18 and 19 respectively; the fourth and seventh decades each contain 10 cases. It will be noted that with advancing age the lines representing gall bladder disease and heart disease approximate each other closer and closer until they coincide in the seventh and eighth decades. Table 2

TABLE 2

Showing the percentage of heart disease in each decade. 109 cases of cholecystitis, 69 heart cases.

3rd Decade .....	46.6%
4th Decade .....	41.6%
5th Decade .....	58.6%
6th Decade .....	79.1%
7th Decade .....	100 %
8th Decade .....	100 %

shows the increasing percentage of heart cases in each decade, beginning with 46.6% in the third decade and

ending with 100% in the seventh and eighth decades.

## OBESITY

There were 57 patients with gall bladder disease who, when judged by clinical standards, considering sex, age, height and weight, were found obese. This represents 52.2% of the entire group. A glance at Chart 1 shows that in contrast to the incidence of heart disease, which increases with the advancing age of the patient, obesity is most frequent during the age period between 30 and 50, totaling 35 or 61% of the entire obesity group. After the age of 50, the tendency to obesity is diminished, but remains at a constant level. Table 3 shows that 62% of all the gall bladder cases in the fourth decade and 64% of the fifth decade, have associated obesity, while in the other age periods it is 40%.

TABLE 3.

Showing the percentage of obesity in each decade. 109 cases of cholecystitis, 57 cases of obesity.

3rd Decade .....	40 %
4th Decade .....	62.6%
5th Decade .....	64.5%
6th Decade .....	41.6%
7th Decade .....	40 %
8th Decade .....	40 %

## OBESITY AND HEART DISEASE

In order to learn what relationship obesity had to myocardial changes of the cholecystitics, we tabulated the number and types of myocardial disease present in this group with particular reference to the age of the patients.

More than half of all the cardiacs (39 or 56.5%) were obese. This corresponds to over 68% of the obesity

cases. Chart 1 shows graphically that the cardiacs with obesity follow the line of the general obesity group, but resemble the total heart group by having an increasing proportion of cardiacs as the age advances. The greatest number, however, occur in the fourth, fifth and sixth decades, totaling 31 cases or 79% of all the obese cardiacs. Table 4 shows the percentage of cardiacs per decade in the obesity group and compares it with the remaining non-obese cardiac cases. In comparing these two groups, one is at once struck with the fact that the chances of having heart disease in association with gall bladder infection are much greater in the fat than the lean, particularly in the fourth and fifth decades of life where it is at least twice as numerous, while after the sixth decade, the chances of having heart disease is about even in both groups. This is shown graphically in Chart 1.

TABLE 4.

Comparing the percentage of heart disease per decade in the obese, and non-obese patients. (57 obese patients, 39 cardiacs) (52 non-obese patients, 30 cardiacs).

	Non-Obese	Obese
3rd Decade.....	44.4%	33.3%
4th Decade.....	22.2%	53.3%
5th Decade.....	36.3%	70 %
6th Decade.....	78.5%	90 %
7th Decade.....	100 %	100 %
8th Decade.....	100 %	100 %

It will be noted that in the third decade the percentage of cardiacs in the obese group is somewhat less than in the non-obese, 33% against 44%. This may be explained by the observation of Master and Oppenheimer<sup>22</sup>, who found that moderate overweight in young patients is an advantage and

that they respond better to cardiac exercise tolerance tests than normal persons.

#### VARIETIES OF HEART DISEASE

In this series, we have failed to meet with cases of definite rheumatic or syphilitic heart disease. We have divided our cases into four groups:

- 1—Chronic myocardial disease.
- 2—Hypertensive heart disease.
- 3—Arteriosclerotic heart disease.
- 4—Combined hypertensive and arterio-sclerotic heart disease.

This grouping is perhaps open to criticism, but there can be no question in anyone's mind as to what is meant by the last three groups. In naming the first group chronic myocardial disease we have taken liberties with the classification of Christian<sup>23</sup> by excluding the evident arteriosclerotic and hypertensive cases. We use the term in the same sense that he does, however, implying that it represents a type of myocardial insufficiency for which no definite etiologic factors are evident. Furthermore, our study suggests that in cholecystitis this is the type of heart which predominates, and is probably caused by the combined action of the infected gall bladder plus obesity.

Table 5 shows the number of heart cases in each group, contrasting the obese with the non-obese. The greatest number belong to the group of chronic myocardial disease;—43 cases or over 62%. The rest comprise 26 cases. The first group is about equally divided between the obese and the non-obese, but the hypertensive and arterio-sclerotic types are about twice as frequent among the obese. Table 6 presents the

TABLE 5.

Tabulating the number of cases in the various types of heart disease in the obese and non-obese.

	Chronic Myo- card. Dis.	Hypert. H.D.	Art. Scl. H.D.	Combined A.S. & Hypert.	Total
Non-Obese .....	21	3	4	2	30 or 43.5%
Obese .....	22	7	6	4	39 or 56.5%
Total .....	43 or 62.2%	10 or 14.4%	10 or 14.4%	6 or 8%	69 or 100%

age groups for the various types of heart disease, showing that the hypertensive and arteriosclerotic types manifest themselves after the 40th year,

coinciding with the usual age incidence for these types of heart disease.

Chart 2 and Table 6 contrast the relative frequency of the cases with

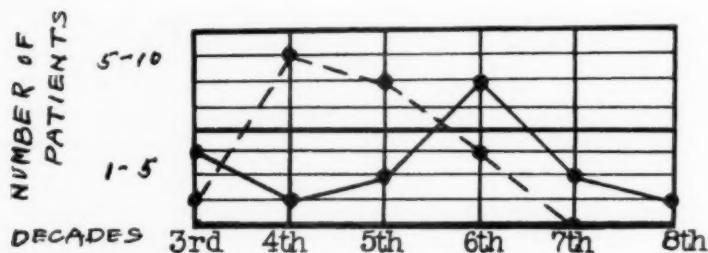


Chart 2. Showing the relative age of 43 cases of cholecystitis associated with chronic myocardial disease in the obese and non-obese.

— — — — Cholecystitis, myocardial disease and obesity.

———— Cholecystitis, myocardial disease, no obesity.

TABLE 6.

Tabulating the number of cases in each group of heart disease, with relation to age and obesity.

		3rd Decade	4th Decade	5th Decade	6th Decade	7th Decade	8th Decade	Total
Chronic	Not							
Myocard.	Obese	4	2	3	7	3	2	21
Dis.	Not	2	8	7	4	1		22
Hypert.	Obese				1	2		3
H. D.	Obese			4	2	1		7
Art. Scl.	Not							
H. D.	Obese			1	1	1	1	4
Combined	Obese			2	2	2		6
Hypert.	Not							
Art. Scl.	Obese				2			2
H. D.	Obese			1	1		2	4

chronic myocardial disease in the obese and non-obese groups, and show quite definitely that in the fourth and fifth decades the obesity cases are far in the ascendancy, while after the age of 50 the preponderating number of cases are in the non-obese group.

RELATIVE FREQUENCY OF HEART DISEASE IN PATIENTS WITH CHOLECYSTITIS AND WITHOUT CHOLECYSTITIS

In an effort to determine with some degree of certainty whether and how much of a rôle cholecystitis plays in the causation of cardiac affections, we

chose at random 109 non-cholecystitic medical cases in identical age groups which were treated in the wards of the hospital, and contrasted the relative frequency of heart disease in this group with the gall bladder group. We excluded no cases except those which were cardiac per se, as rheumatic fever, subacute and acute endocarditis and so on.

Chart 3 and Table 7 shows that the non-gall bladder patients have a much less incidence of cardiac disease—41% as against 63% in the cholecystitics. The gall bladder heart cases almost double and quadruple the non-

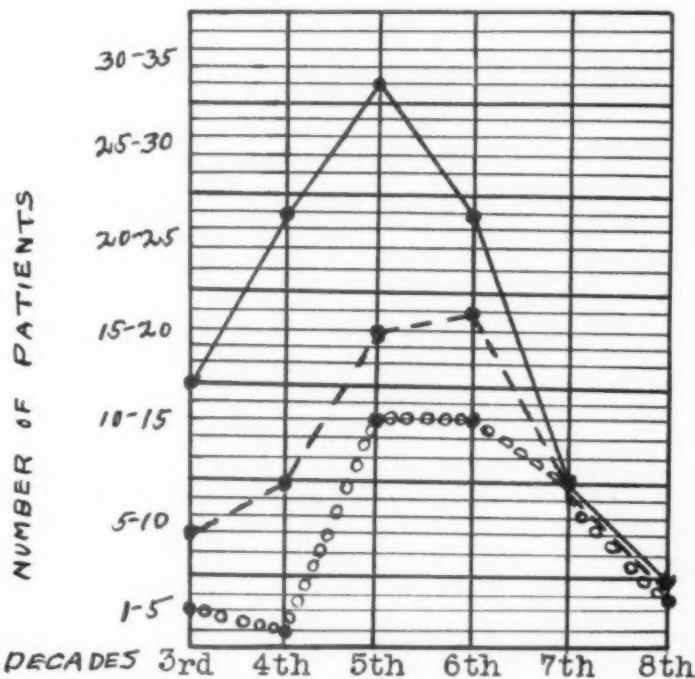


Chart 3. Contrasting the incidence of heart disease in 109 cholecystitics against 109 non-cholecystitics.

69 cholecystitics with heart disease.

5 non-cholecystitics with heart disease.

———— Cholecystitics.

- - - - - Cholecystitics with heart disease.

o o o o o Heart disease without cholecystitis.

TABLE 7.

Showing the percentage of heart disease per decade in 109 patients without cholecystitis; comparing it to 109 patients with cholecystitis and 52 non-obese patients with cholecystitis.

	Non Gall B.	Chole- cyst.	G.B. with- out Obes.
3rd Decade	20 %	46.6%	44.4%
4th Decade	8 %	41.6%	22.2%
5th Decade	41.9%	58.6%	36.3%
6th Decade	54.1%	79.1%	78.5%
7th Decade	100 %	100 %	100 %
8th Decade	80 %	100 %	100 %

gall bladder cases in the third and fourth decades respectively, with about 20% greater frequency in the fifth and sixth decades, but both groups are about even in the seventh and eighth decades. Lest it be assumed that the reason for the preponderating number of heart cases in the cholecystitic group is due to its associated obesity, we have appended the third column in Table 7 which consists of our non-obese gall bladder cases with cardiac affections. This latter group, in its percentage of heart cases also exceeds by a great margin, those individuals

who have no biliary disturbance. An exception is present in the fifth decade, in which there is a slight preponderance of heart cases in the non-cholecystitics.

#### THE RELATION OF THE SEVERITY OF CHOLECYSTITIS TO THE SEVERITY OF THE CARDIAC AFFECTIONS

Table 8 indicates that 44% of the 109 gall bladder cases belong to the severe group of cholecystitis as judged by biliary colic, jaundice and other clinical data. Well-marked heart disease, based on the finding of more than moderate hypertrophy, or electrocardiographic evidence of marked myocardial or coronary disease, or decompensation, numbered 49 or 71% of all the cardiacs. There was a total of 11 or 15.9% with decompensation. It will be noted that there was no apparent difference in the effect upon the heart in the mild or the severe cholecystitics. In order to determine the relative effect of mild or severe cholecystitis on the hearts of the younger individuals, we studied this relationship in the pa-

TABLE 8.

Showing the relative frequency of clinically mild and severe cholecystitis with relation to moderate and well marked heart disease, and decompensation.

	Total
60 or 55.1% of the 109 cases had mild cholecystitis.....	109 cases
49 or 44.9% of the 109 cases had severe cholecystitis.....	or 100%
30 or 61.2% of the 49 severe cholecystitics had h. d.....	69 cases
39 or 65 % of the 60 mild cholecystitics had h. d.....	or 100%
22 or 73.3% of the 30 cardiacs with severe chole. had well marked heart dis.	49 cases
27 or 69.2% of the 39 cardiacs with mild chole. had well marked heart dis.	or 71%
5 or 16.6% of the 30 cardiacs with severe chole. had decompensation.....	11 cases
6 or 15.3% of the 39 cardiacs with mild chole. had decompensation.....	or 15.9%
23 or 58.9% of the 39 cases in the 3rd & 4th decades had mild cholecystitis	39 cases
16 or 41.1% of the 39 cases in the 3rd & 4th decades had severe cholecystitis	or 35.7%
11 or 47.8% of the 23 mild cholecystitics in the 3rd and 4th decades had heart disease .....	17 cases
6 or 37.5% of the 16 severe cholecystitics in the 3rd and 4th decades had heart disease .....	or 24.6%



tients in the age period between 20 and 40, but found no appreciable difference. In this respect our studies are in agreement with those of Willius and Fitzpatrick<sup>20</sup> who also found that there was no relationship between the degree of pathology in the heart and that in the abdomen.

It should be remembered, however, that the designation "severe cholecystitis" is only relative. It might be severe from the standpoint of pain or other physical discomforts, yet pathologically it may be of minor consequence. It is also well to remember that a mild cholecystitis from the standpoint of the patient or even the physician, may, because of its long duration and insidious character, cause more damage to the heart than the more explosive type of gall bladder.

#### MALE PATIENTS

Aside from the fact that cholecystitis in the male is infrequent when compared to the female—16 or 15.5%, there are certain other findings in the male which deserve attention. Analysis

of Table 9 shows that the incidence of cholecystitis increases after the fifth decade—9 or 56% of the cases occur after the age of 50, while in women at the corresponding age, it is only 32%. Heart disease in this group total 12 or 75% as against 61% in the women. Decompensation occurred in 5 or over 41.6% of the heart cases, and 8 of the 12 or 66.6% had severe heart symptoms. The arteriosclerotic type of heart predominated—7 or almost 60%. Obesity was present in 6 or 37.5% as contrasted to 55% in the female group. The severe types of cholecystitis as represented by symptoms, physical and laboratory findings numbered 10 or 62%.

From this table one is tempted to draw the conclusion that when a male is subject to cholecystitis, it is more apt to occur at a later period of life, to be more severe and associated with a marked degree of myocardial involvement.

#### DISCUSSION

Comparing our findings with those of Willius and Fitzpatrick<sup>20</sup> and

TABLE 9.  
Data concerning 16 male patients with cholecystitis.

Decades	3rd	4th	5th	6th	7th & 8th	Total Number
No. of Pts.....	2	3	2	4	5	16
Heart Disease .....	0	1	2	4	5	12
Art. Scle. H. D.....			1	3	3	7
Hypertensive .....						0
Comb. H. & A. S.....			1		2	3
Chronic Myoc. ....		1		1		2
Decompensation .....			1	2	2	5
Card. Symp.—Severe .....		1	1	2	4	8
"    "—Mild .....			1	2	1	4
"    "—None .....	2	2				4
Obesity .....			1	2	3	6
Diabetes .....					1	1
Cholecystitis—Mild .....	1	2	1	1	1	6
"—Severe .....	1	1	1	3	4	10

Leech<sup>21</sup>, we discover a great discrepancy in the percentage of cardiac affections. Willius and Fitzpatrick report 39%, and Leech 25% of heart disease in their respective series. Our group, as already stated contains 63.3% of heart cases. In a study of coronary sclerosis with an analysis of 86 necropsies, Willius and Brown<sup>24</sup> found diseased gall bladders associated with coronary sclerosis in 24% of the cases. When one realizes that demonstrable coronary sclerosis is found in but a minority of the diseased hearts of patients affected with cholecystitis, it is not difficult to believe that 25% or 39% are extremely low figures. In a study of 1000 cases of obesity, Preble<sup>25</sup> found 66.2% with cardiac impairment. Master and Oppenheimer<sup>22</sup> in 99 cases of obesity, found that 51% had enlarged hearts and 67% had hypertension. Terry<sup>26</sup> studying 63 patients with obesity found hypertension in 58%. Now, taking into consideration the great number of patients with obesity in the three groups of cholecystitis under consideration, 45% (Willius and Fitzpatrick) 67% (Leech) and 52% (ours) respectively, one may more easily be reconciled with the finding of 63.3% of myocardial disease in our series of 109 cases of cholecystitis.

It is interesting to speculate on the relative effect of obesity or chronic cholecystitis upon the hearts of patients with cholecystitis. Leech<sup>21</sup> and others conclude that obesity is responsible, while Willius and Fitzpatrick<sup>20</sup>, Strauss and Hamburger<sup>17</sup>, Mayo<sup>18</sup>, Babcock<sup>10</sup> and others believe that since the patient's myocardium improves after gall bladder surgery, it is proof that the infected gall bladder exercises

a deleterious influence upon the heart.

Our own analysis indicates, we believe, that both factors are responsible. The responsibility of the infected gall bladder is suggested by the evidence of greater preponderance of heart disease in the non-obese cholecystitic cases than in the control group of non-cholecystitic cases. The responsibility of obesity is adduced by the evidence that there is a larger number of heart cases in the obesity group, particularly in the age period between 30 and 50. Another fact helps to throw light on the situation. It is claimed by Cabot<sup>27</sup>, and not without good reason, that most cases of chronic myocardial disease, in which the blood pressure is low, were originally hypertensive, but that as the myocardium broke under strain, it underwent dilatation, with consequent low tension. That hypertension is prominently associated with obesity is a matter of common knowledge and is proven by the studies of Master and Oppenheimer<sup>22</sup>, Terry<sup>26</sup> and others. In our series, although 56.5% of all cardiacs were obese, yet there was hypertension in only 23% of all the cardiacs and in 28.2% of the cardiacs with obesity. Our interpretation is that the infected gall bladder aggravates the already affected myocardium of the obese.

At this point the question may be asked, as to what influence focal infection may exercise on the hearts of cholecystitics. In this series practically every patient had some form of focal infection. The group of non-cholecystitic patients had a similar incidence of focal infection. It is our impression that this finding is the rule in practically every well studied group of

ward patients. This study is not competent to draw conclusions in this matter, yet there is no known reason to suppose that focal infection would affect cholecystitis differently than patients with other types of disease.

The high percentage of myocardial involvement in the older patients with cholecystitis, particularly in the seventh and eighth decades, is clearly brought out in this study. The control group, without cholecystitis, presents a similar condition. No doubt, the natural processes incident to old age, may be held accountable for this phenomenon.

The small number of male patients in this series, should make one wary of accepting in toto the findings of Table 9; yet we think it is significant. In this connection it may be of interest to mention, that of the twelve cases which Babcock<sup>9</sup> reported in 1909 showing the serious effect of cholecystitis upon the circulation, ten were males.

#### SUMMARY AND CONCLUSIONS

1. 109 patients with chronic cholecystitis were studied.
2. 63.3% had associated myocardial disease, of which 56.5% were combined with obesity.

3. 52.2% of the entire group were obese.

4. 68% of the obese patients had heart disease.

5. In the fourth and fifth decades the incidence of heart disease was greater in the obese.

6. Hypertension was present in 28.1% of the cardiacs with obesity, and in 16% of the cardiacs without obesity.

7. 62.3% of the cardiacs were of the chronic myocardial variety, and were not accompanied by arteriosclerosis or hypertension.

8. 71% of the cardiacs were well marked cases of which 15.9% were decompensated.

9. Clinically severe cholecystitis did not differ from clinically mild cholecystitis in its effect upon the heart.

10. Males are less frequently subject to cholecystitis than females, and in this series were older, ran a more severe course, and had greater cardiac damages.

11. It is adduced, from data obtained in this study, that the infected gall bladder and obesity are equally responsible for the myocardial damage of patients with chronic cholecystitis.

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# Cessation of Attacks of Auricular Paroxysmal Tachycardia by the Use of Calcium

## Preliminary Report

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and  
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THE object of this paper is to report a series of five cases of auricular paroxysmal tachycardia, three of which were successfully arrested by the use of calcium intravenously. In all three cases the paroxysms ended suddenly, almost dramatically, the normal rhythm being immediately restored. In two of the three cases, electrocardiograms were taken during the administration of the drug and show the sudden transition.

These facts are of interest because no method of treatment so far known is always uniformly successful in stopping paroxysms. It has been our experience, as indeed that of all who have treated many cases of auricular paroxysmal tachycardia, that in certain subjects the numerous procedures with which we combat the rapid rate remain unavailing at one time or another.

Aside from the extreme mental perturbation, paroxysmal tachycardia carries with it two dangers: First, the patient may die during the attack. Fortunately, this is rare. Lewis<sup>1</sup> who

has had exceptional opportunities for observation in this field, states that no fatal termination has come within his experience unless in the patients who were gravely ill previous to the attacks. Secondly, the attacks may become so frequent that they finally exhaust the heart muscle and lead to death from myocardial failure.

Before referring to the methods we use, it is desirable to review briefly the various measures at our disposal for terminating attacks of paroxysmal tachycardia. They are essentially:

1. Stimulating of the vagus, either directly or indirectly.
2. The use of certain drugs.

### STIMULATION OF THE VAGUS

This may be obtained by (a) making the patient hold a deep breath; (b) causing him to gag or vomit; (c) ocular compression; and (d) vagal pressure. Whether pressure on the carotid sheath constitutes direct vagus stimulation may be seriously questioned in the light of recent work. Hering<sup>22</sup> has recently presented evidence showing that the slowing produced by so-called vagal pressure is the result of a reflex originating in the

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region of the carotid sinus rather than in direct vagus stimulation and Erben states that compression of the jugular veins stimulates the vagus simply by raising intracranial venous pressure.

#### THE USE OF CERTAIN DRUGS

Recently, quinidine given intravenously has proved successful in stopping attacks of paroxysmal tachycardia. Singer and Winterberg<sup>2</sup> report a series of nine cases, including one of ventricular tachycardia, thus treated. The doses were 0.4, 0.5, and 0.75 gm. The average dose is 0.5 gm. In six of the cases the paroxysmal attack was brought to an end after an interval varying from a few seconds to ten minutes after the injection. In four of these six cases there was a slowing in the heart rate before the return to the normal mechanism. Boden and Neukirch<sup>3</sup> treated six cases by intravenous injections of quinidine. The attacks ended abruptly in four and slowed in two cases.

Iliescu and Sebastini<sup>4</sup> report a case with frequent, short paroxysms where quinidine gradually lowered the rate, while it increased the length of the paroxysm until the normal rhythm was resumed. Many observers, Parkinson and Nicholl<sup>5</sup>, Lean<sup>6</sup>, Ottol<sup>7</sup>, Wolferth<sup>8</sup>, Sprague and White<sup>9</sup>, and others have reported excellent results with the use of quinidine by mouth, not only as a preventive of attacks, but as favorably influencing the paroxysms itself. However, failures are not unknown. In the case of Otto and Gold<sup>10</sup> quinidine failed to stop the attacks occurring spontaneously or those induced by epinephrine.

While the great expectations awakened in the beginning by quinidine in paroxysmal tachycardia have not completely materialized, this remedy has proven to be of definite value. Sprague and White<sup>9</sup> conclude that it is effective in about one half the cases of auricular paroxysmal tachycardia in preventing the recurrence of paroxysms.

Other drugs have also been of service occasionally. Digitalis is of value to ward off attacks and may be useful when other measures, including quinidine, have failed. It is important as pointed out by Levine and Blottner<sup>11</sup> that full doses be given—failures being sometimes due to insufficient amounts. De Meyer<sup>12</sup> states that small doses of physostigmine associated with strophanthus are effective in auricular paroxysmal tachycardia, but have no effect in ventricular tachycardia.

Schuster<sup>13</sup> reports a case of simple paroxysmal tachycardia with a pulse rate of 180 per minute, the patient being in extremis as a result of its long duration. As a last resort he gave the patient 1 c.c. of adrenaline hypodermically. This bringing only very little response, he gave 1 c.c. of the same intravenously after which the pulse rate dropped to 80. Such slowing, however, was preceded by a period of marked cyanosis during which it appeared that the patient would expire. While the result was prompt, the reaction was unusually marked.

Dukes<sup>14</sup> records a case of paroxysmal tachycardia in which the attacks occurred once or twice a week. He gave parathyroid gland gr. 1/10 t.i.d. The effect, he states, was dramatic for the moment and by continuing the tablet medication, the patient



has been free from distressing paroxysms for some years. Corney<sup>15</sup> reports a similar case in which all other methods having failed, parathyroid gland was used, 1/10 gr. of dried gland, t.i.d. on an empty stomach and the medication was continued up to the time of report. The paroxysm ceased on the third day and during the subsequent month, only three attacks occurred. Since it has not been definitely proved that parathyroid administered by mouth has any therapeutic effect, the conclusions to be drawn from these two reports are rather questionable.

Aside from the above methods which aim directly at stopping the paroxysm or preventing its recurrence, palliative measures, such as morphine, chloral, bromides and luminal are of value in calming and sedating the patient. It should not be forgotten that when attacks are induced by provocative factors, such as excitement or gastric distention, the latter particularly should be corrected whenever possible.

In our series we gave calcium intravenously in an attempt to stop the paroxysm of tachycardia. This drug has as far as we know not been previously used for this express purpose. The following are the case reports of our patients treated with calcium:

*Case 1.* L.P., female, age 50. Patient had no definite cardiac abnormality clinically. She suffered from attacks of paroxysmal tachycardia for several years, of which a chronic cholangitis might have been a causative factor. The attacks usually lasted from one to three days. In 1926, during a paroxysm calcium was administered. Since immediate cessation of the attack was not expected, we did not take an electrocardiogram during the period of transition. The normal

heart rate was resumed almost immediately after the injection as shown on electrocardiogram taken 10 minutes later.

*Case 2.* M.B., male, age 40. Patient had no cardiac abnormality that could be recognized clinically. He was brought to the hospital in an attack while he was driving a car. He gave a history of similar attacks which lasted from 6 to 12 hours. Calcium was administered. There was no immediate effect. Except for a slight slowing of the cardiac rate, no change was noted afterwards.

*Case 3.* B.B., female, age 48. She was diagnosed as rheumatic mitral stenosis with slight cardiac enlargement, but no evidence of decompensation. She gave a history of attacks of paroxysmal tachycardia, lasting from several hours to several days. Two and a half years ago, patient came to the clinic one and one half hours after an attack commenced. Two ampules of calcium were administered and cardiographic records were made. The effect was remarkable, practically instantaneous. The tracing (Fig. 2) shows the changes as they occurred.

*Case 4.* R.T., male, age 45. This patient was a case of post-rheumatic mitral valvulitis with slight cardiac enlargement but no decompensation. He had frequent attacks of paroxysmal tachycardia which usually lasted several days. After calcium was administered, he commenced to vomit and perspire. The attack did not cease immediately, but a definite slowing of the cardiac rate was noted and within one half hour, the normal rhythm was resumed.

*Case 5.* B.T., female, age 45. Patient was diagnosed as arteriosclerotic heart disease with cardiac enlargement. She suffered from attacks of paroxysmal tachycardia for several years. The attacks usually lasted from one to three days. Calcium was administered intravenously. Sino-auricular block (Fig. 3) was induced and then the normal rhythm was re-established.

In the above series of cases, the patients were given calcium in the form of afeuil or calcium gluconate. The

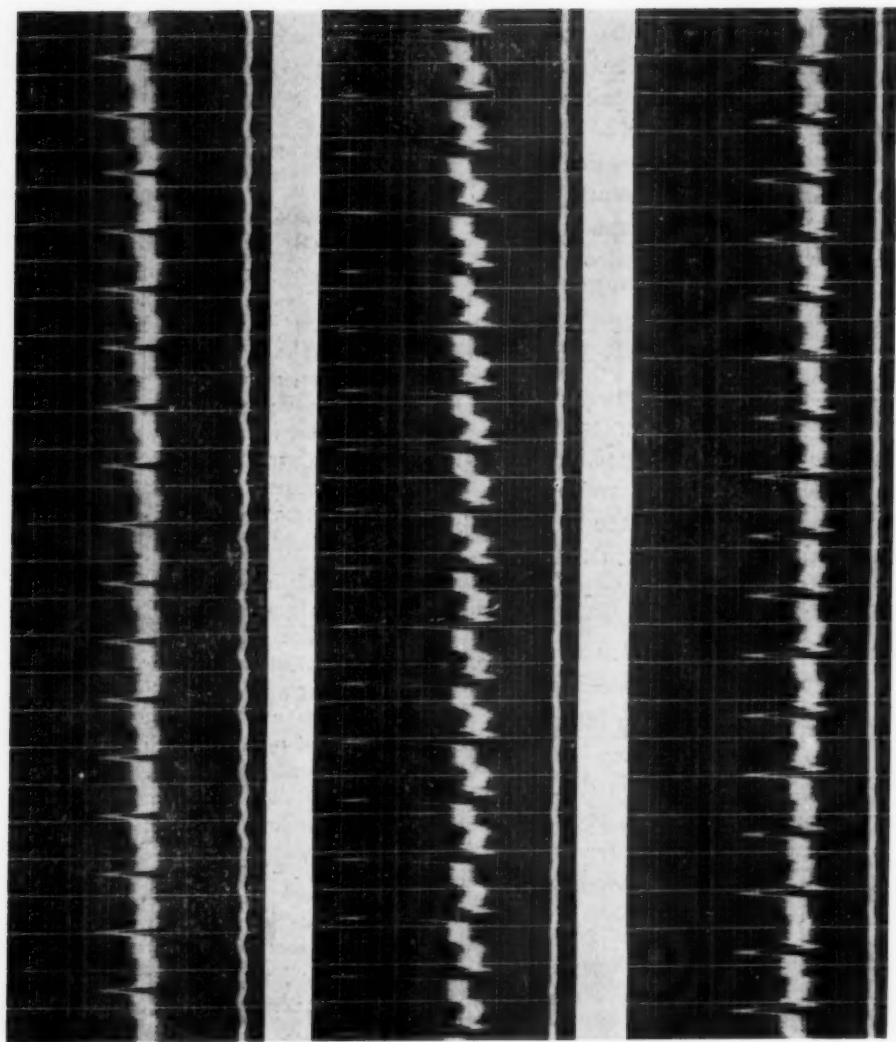


Fig. 1a

CASE 1: Fig. 1. Tracing A shows an attack of auricular paroxysmal tachycardia, rate 187.5 per minute. An ampoule of atropine was administered intravenously and towards the end of the injection a definite slowing of the pulse rate was noted. The electrodes were immediately attached to the precordial leads. Tracing B was then taken (probably five to seven minutes after the injection) and shows the return to normal rhythm, rate 187.5 per minute.

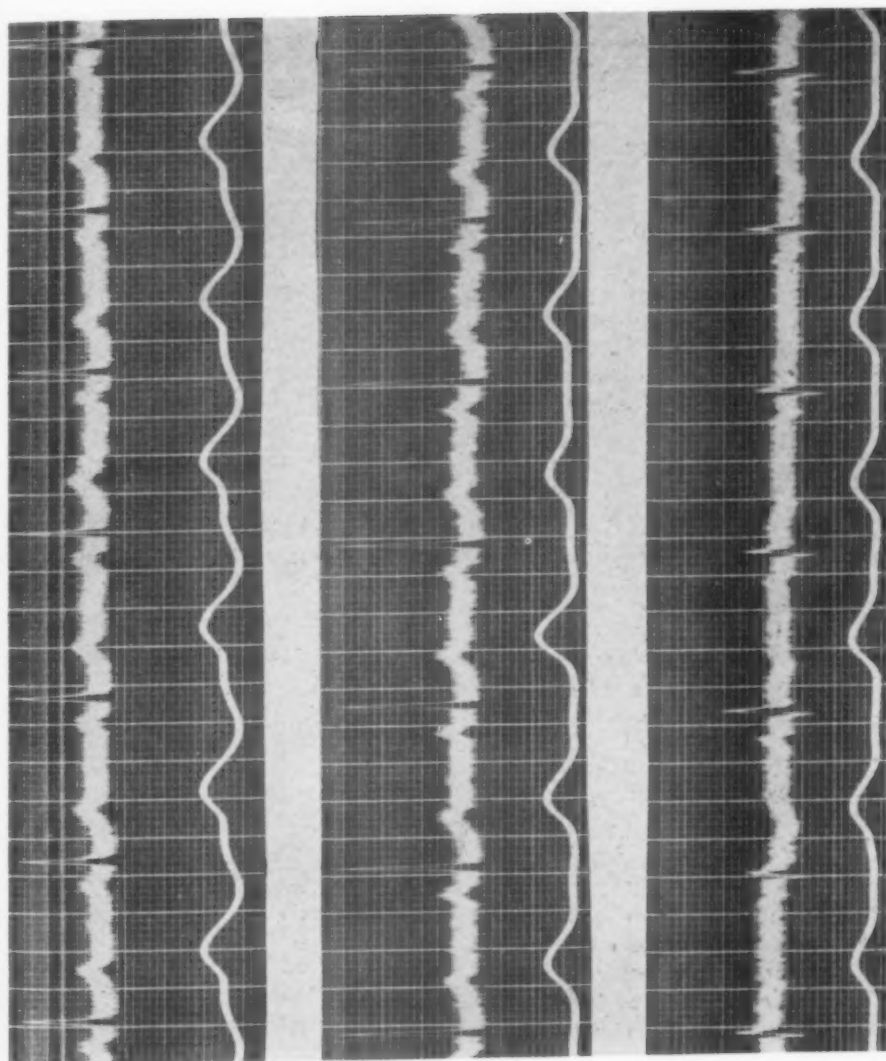
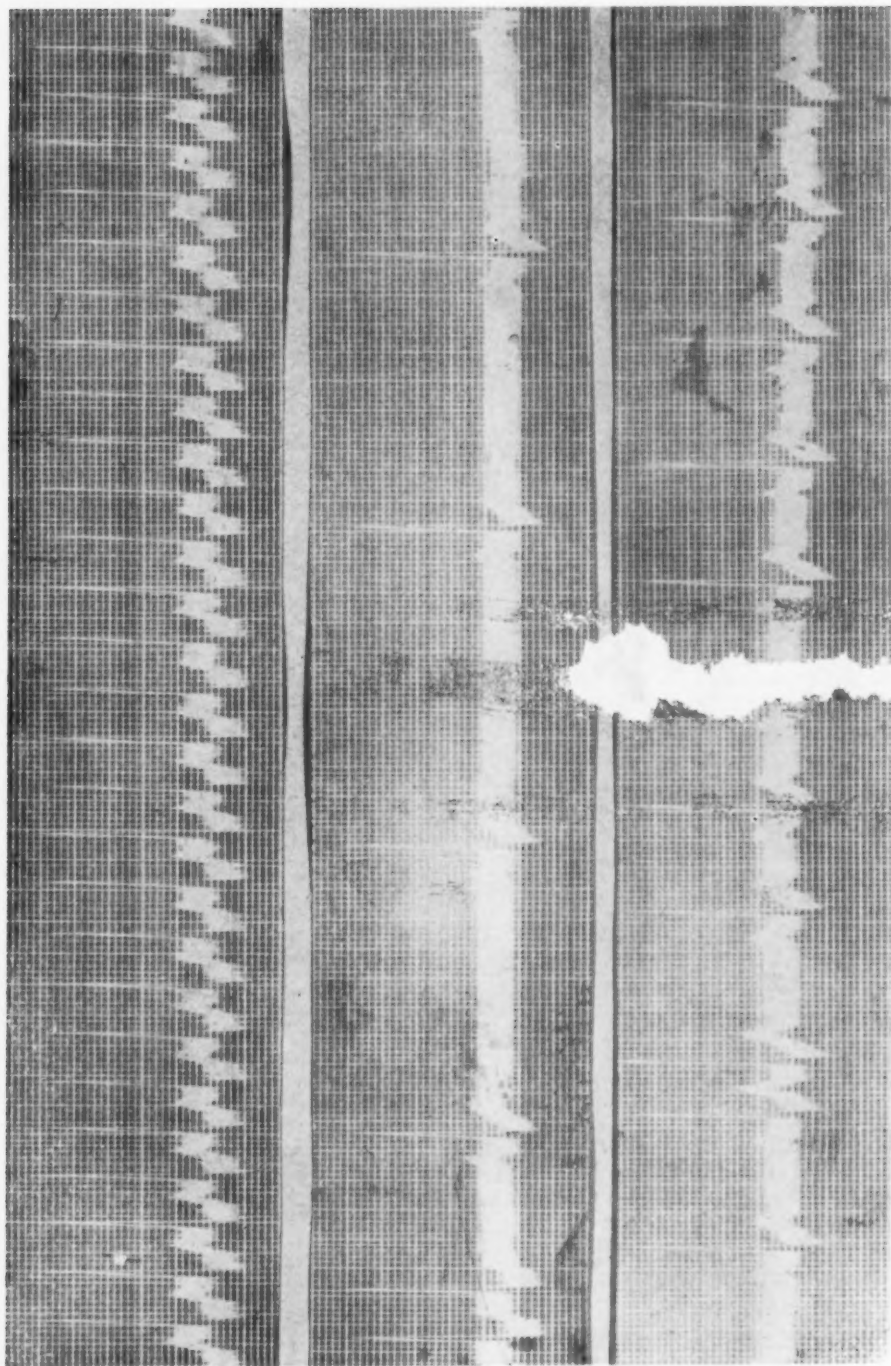


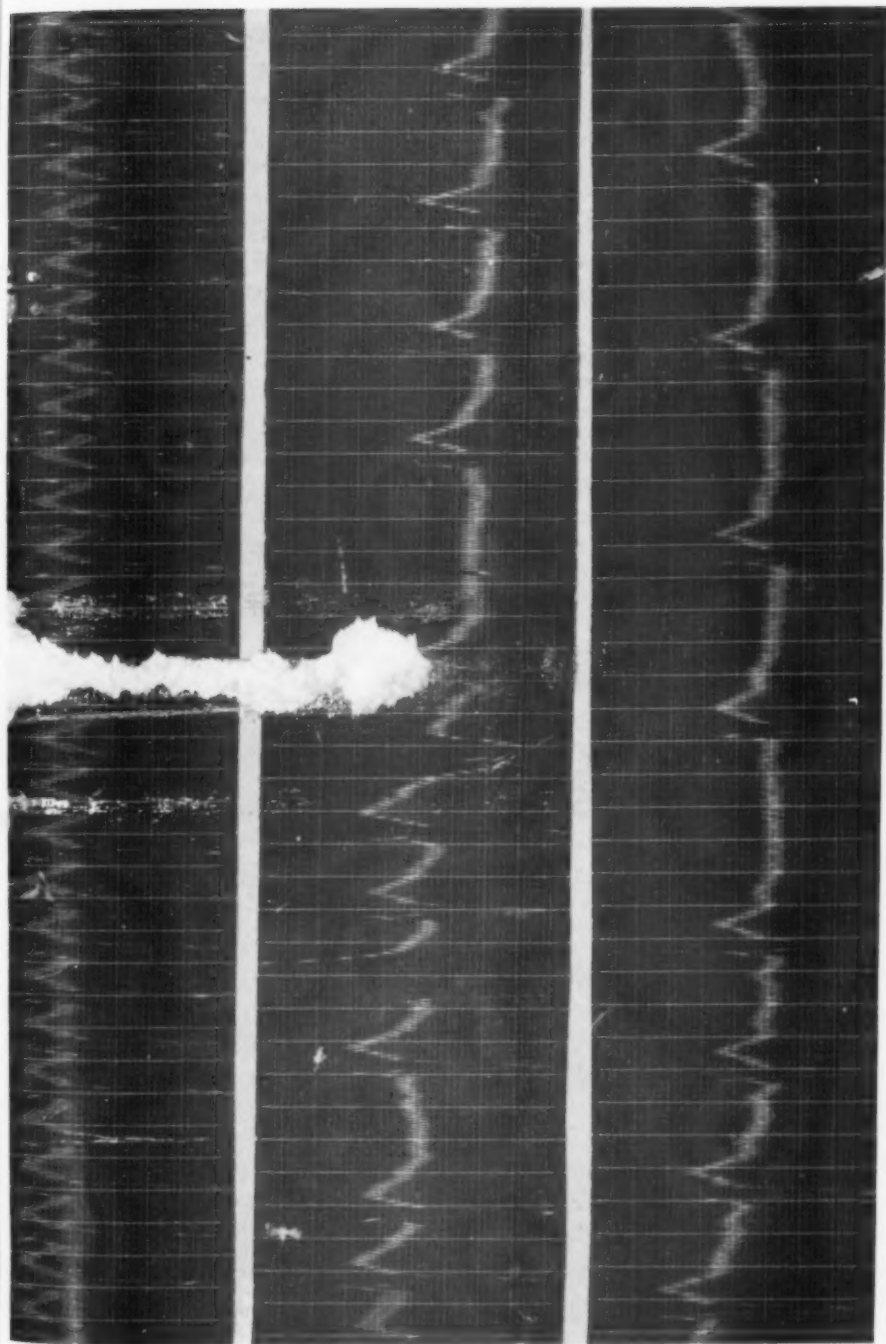
Fig. 1b

electrocardiograph. Tracing B was then taken probably five to seven minutes after the injection) and shows the return to normal rhythm (28 per minute).



CASE 3: FIG. 2. A continuous tracing showing paroxysm of tachycardia. At the end of the injection, the rate slowed suddenly, a sinusoidal rhythm was then resumed. At the beginning of the paroxysm, the rate was 180 per minute.

hyocordina and the effect of 2 ampoules of atropine. Towards the end of the injection, the rate slowed suddenly, a sinusoidal rhythm was then resumed. At the beginning of the paroxysm, the rate was 180 per minute and within 15 seconds it was 72



CASE 5; FIG. 3. A continuous tracing showing a paroxysm of tachycardia, heart rate 200 per minute. Towards the end of the injection the rate suddenly slowed and a series of events followed simulating those in Fig. 2. The sino-auricular block, however, was of longer duration than in Fig. 2. The normal rhythm was resumed in three minutes. (Tracing is not very clear, due to restlessness of patient.)



remedy must be injected slowly, about five minutes being required to inject 20 c.c. During its administration, the patient complains of a sense of intense heat, constriction in the throat, sometimes nausea or burning in the rectum; but all these symptoms are evanescent, passing away in a few minutes. In three cases, the paroxysms ended almost immediately after the calcium was administered and the return to normal rhythm was abrupt as shown by the accompanying electrocardiograms. Cases 1 and 3 received follow-up treatment in the form of calcium lactate, gr. XX, t.i.d. They have been free from attacks since, but whether this is due to the calcium cannot definitely be stated.

In view of the remarkable results obtained, one may pertinently inquire as to the probable mechanism of action of this remedy. Calcium acts on the cardiac muscle by promoting its state of tonic contraction<sup>16</sup>. When present in quantities above normal, or when in relative excess over potassium ions, it causes a condition of tonic contractions which has been designated as calcium rigor. Brule<sup>17</sup>, has shown that large doses of calcium induce in the isolated mammalian heart first an increase in rate, later A.V. block and finally stoppage in diastole.

Walter and Bowen<sup>18</sup> observed after intravenous injections of calcium in normal dogs an initial increase in the heart rate with no change in blood pressure. Large doses, however, caused extra-systoles, tachycardia and changes in conduction. We have noted these effects in our experiments.

Singer<sup>19</sup>, concludes from observations on intravenous administration of

calcium chloride that there is a temporary slowing and strengthening of the heart beat with some decrease in the blood pressure and Lowenberg<sup>20</sup> reports that repeated doses of calcium exert a beneficial effect upon the heart which he terms "cardiotonic."

The mechanism of simple paroxysmal tachycardia is not yet absolutely known. It is supposed to occur as a result of the establishment of an abnormal focus in the auricle. The theory has been advanced recently that it is a form of circus movement.

While the action of calcium on the heart muscle has not been entirely ascertained, it appears generally decided that an over-abundance of calcium ions acts by promoting its state of contraction. Such an action, if at all marked, would work in the direction of increasing the refractory period of the auricular muscle thus tending to inhibit the formation of the ectopic impulse and giving the pace-maker an opportunity to reassert itself. If this is the manner in which calcium, given intravenously acts in stopping a paroxysm of tachycardia, this part of its action at least would be analogous to that of quinidine.

It is interesting to note that whereas in most reported cases where the termination of attacks of paroxysmal tachycardia have been noted, the termination occurs by a post paroxysmal pause, followed by immediate resumption of normal rhythm. In our two cases, after calcium there was a considerable pause in the initial beats following the paroxysm which gradually diminished in the succeeding beats and finally gave way to the normal rhythm.



## CONCLUSIONS

1. An attempt has been made to review briefly the different methods of treating an attack of simple paroxysmal tachycardia.

2. A series of three cases of simple tachycardia is reported with electrocardiograms in which the paroxysms were immediately terminated by the use of calcium. It is believed that this is a therapeutic measure which while not successful in every instance, is well worth trying where other methods have failed and where the length of the attack is dangerously prolonged.

3. There is some evidence that administration of calcium by mouth between attacks tends to lessen the number of paroxysms.

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Since this paper has been sent in for publication, one of us has observed a case of ventricular paroxysmal tachycardia in whom death occurred a few minutes after the intravenous injection of calcium chloride (10 c.c. of a 10% solution). This case was not treated under our direction. The patient was 68 years of age with an advanced grade of arteriosclerotic heart disease and was almost in extremis. The drug used was calcium chloride which has a greater toxicity than either afenil or calcium gluconate; it was given rapidly through a large bore needle instead of slowly and the patient had been previously heavily digitalized. These may all have been factors in the final result. Calcium is given intravenously for many conditions and fatalities are extremely rare. However, we deemed it advisable to note this occurrence in our paper, which is the only one which has come to our attention.

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# The Diagnosis of Gastric Lesions by Intra-Gastric Photography

## Preliminary Report\*

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THE X-ray examination of the stomach with the barium meal reveals merely a shadow picture of the barium mixture as limited by the gastric walls and borders. Hence, when a defect in the upper or lower border occurs it is filled by this fluid mixture and thus its shadow is outlined. Again, this fluid mass also lends itself to distortion by peristalsis or any irregularity in the stomach wall caused either by an organic disease or a simple spasm of the wall.

From the pioneer work of Hemmeter, Rieder, Holzknacht and others it was soon discovered that lesions on the anterior and posterior walls of the stomach are, by this method recognized with difficulty and often not at all. This is because the opaque mixture fills the entire stomach, thus obscuring any defect that may be present in its walls. Many attempts have been made to diagnose such lesions by variations in the technique during the X-ray examination. By manual compression of the abdomen during fluoroscopy or by giving small amount of the barium mix-

ture and watching the course of the rugae, filling defects may sometimes be noted in the anterior or posterior walls. Ulcers have often been found by these methods. Many more have been missed, especially when they were shallow or situated in unfavorable positions among the thickened and at times hypertrophied rugae at the pylorus.

For many years gastroscopy has been used in an attempt to visualize the lesions of the interior of the stomach. But the natural limits of the field of available vision and the unwillingness of many patients to submit to the difficult procedure involved, has prevented the full use of the gastroscope. Consequently, there has long been a feeling among gastro-enterologists that some method should be devised to picture the interior of the stomach on a photographic film, by means of a camera inserted through the esophagus into the stomach. Naturally, such a camera would have to be no wider than an ordinary stomach tube and be in some way connected with a proper source of light of adequate intensity so that photographs could be taken. Such an instrument has actually been devised by Mr. Bach working under the

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FIG. 1. Gastro-Photograph with camera.

direction of Professor Porges and Dr. Heilpern at the Wenckebach clinic in Vienna.

This instrument, Fig. 1, consists essentially of a semiflexible tube carrying at its distal end a double camera, an upper and lower, between which is a small electric bulb so constructed that when activated by a transformer it yields a bluish white light of 12,000 candle power for  $1/120$  of a second and is then destroyed. The transformer takes its energy direct from the house lighting current. Each camera contains four small films regularly disposed in a circle; and by means of two pinpoint holes, an upper and a lower, a stereoscopic picture is taken by each film of a 90 degree arc of the circumference. Thus at one exposure eight double stereoscopic views are taken. These eight films are so marked that when developed one can readily tell which part of the circumference of the stomach is pictured on the film.

These pictures are, of course, best taken on the fasting stomach which

should be further evacuated from its overnight secretion. This is accomplished by introducing a double stomach tube and placing the patient on the left side in the trendelenberg position. Through this tube the stomach is first filled with air, then one side of the stomach tube is released and through the other side air is continually pumped so as to keep the stomach from collapsing. The tube is then withdrawn slowly and in this manner the stomach is completely emptied. In cases of overnight food residue the stomach is first thoroughly washed out and then emptied as outlined above.

The patient is then placed before a fluoroscope, the gastro-photor camera is introduced and its position localized. The stomach is then inflated with air through a special opening in the tube. The shutter is opened, the transformer button pressed, the shutter closed and the camera is withdrawn. The whole procedure from the moment of introduction of the camera to the time of its withdrawal should not be more than

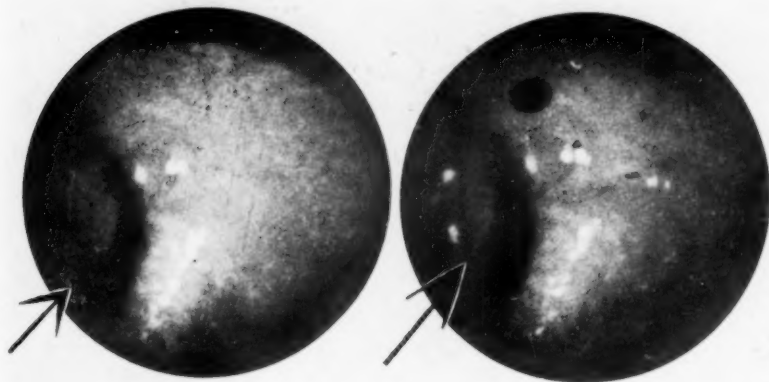


FIG. 2. Showing a carcinoma of the pars pylorica proven at operation.

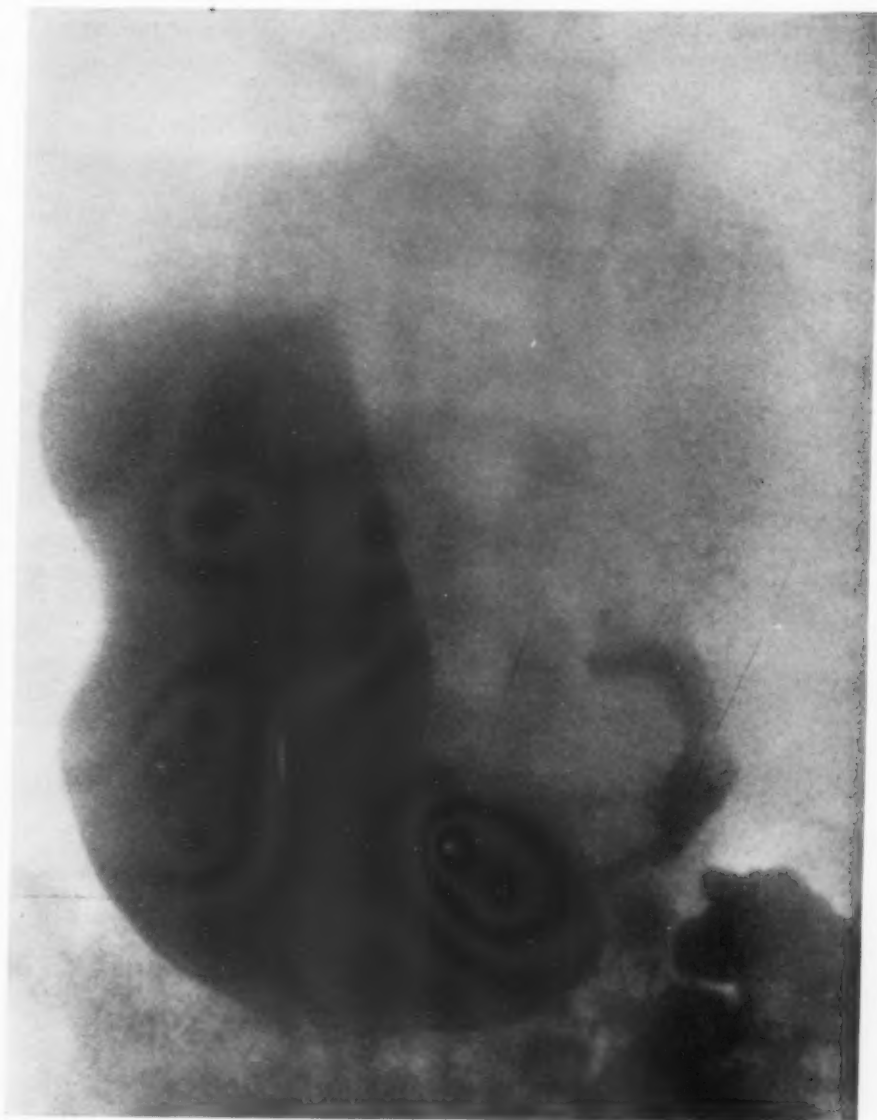


FIG. 2A. X-ray of carcinoma shown in Fig. 2.

$\frac{1}{2}$  to 1 minute. The films are then removed from the camera in a dark room, developed and enlarged to about ten times their original size. These pictures should be studied in detail. Proper skill is easily acquired after comparing a number of these pictures with surgical and autopsy material wherever available.

This report is limited to the first twenty-five cases in which we carried out this procedure. In the beginning we had a few unsatisfactory results but as our technique improved our pictures were uniformly good.

Four of our series were operated upon. In three of these cases the diagnosis was made on the roentgenological findings and confirmed by the gastro-photor pictures, Figs. 2, 2A, 3, 3A, 4. In the fourth case, No. 38082, the roentgenological films were negative. The fluoroscopic examination showed a suspicion of pathology at the pylorus. The gastro-photor pictures showed definitely the presence of two ulcers at the pyloric region. Though the opera-

tion in this case was performed by an experienced surgeon, he was unable after opening the stomach to feel the ulcers with his finger reaching to the pylorus. Upon autopsy, however, the gastro-photor diagnosis was confirmed and the two ulcers found, Figs. 5, 5A, 5B.

Of the twenty-one cases not operated upon, two gave evidence of prepyloric ulcer on the X-ray films. In these two cases the gastro-photor pictures showed only the presence of spasm of the gastric wall, Fig. 6.

*Case No. 37470.* Diagnosed as gastric ulcer, was confirmed by fluoroscopic examination which showed an incisura with a niche on the posterior wall near the lesser curvature. The gastro-photor pictures did not show the ulcer but gave evidence of hypertrophied rugae among which a small ulcer could easily be hidden so that it could not be visualized on the picture, Fig. 7.

*Case No. 37345.* On X-ray showed a limited mobility of the pars pylorica but no definite defect was observed. The gastro-photor pictures revealed an ulcer near the pylorus, Fig. 8.

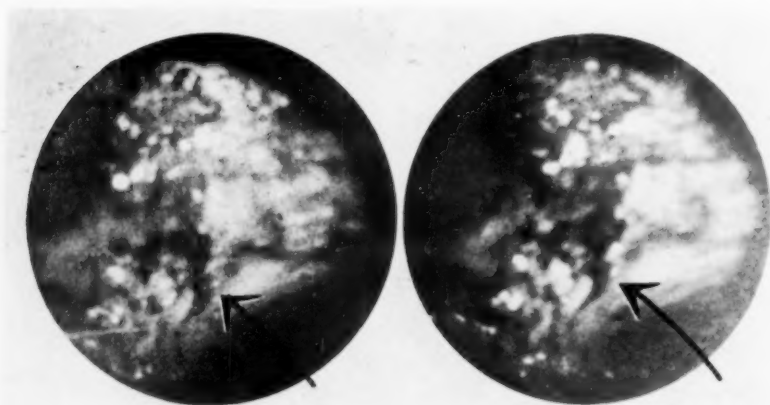


FIG. 3. Carcinoma involving the lesser curvature and pylorus. Proven at operation.





FIG. 3A. X-ray of stomach showing carcinoma in case shown in Fig. 3.

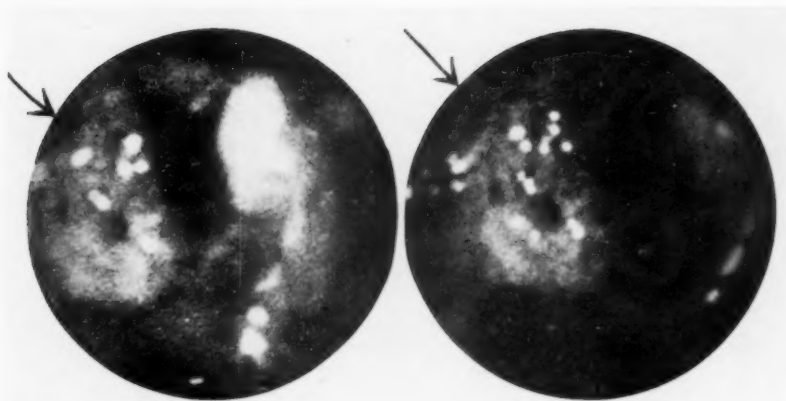


FIG. 4. Case No. 36764 showing ulcer on lesser curvature near the cardia, proven at operation.



FIG. 5. Case No. 38082 showing two ulcers on the lesser curvature not found on X-ray or at operation but found at post mortem.

*Clinic Case No. 501.* Where patient complained of gastric disturbances with definite history of sour eructations; epigastric pain coming on from one hour to one and one half hours after meals and relieved by food and soda and often by vomiting. Occasionally the patient noticed blood in the vomitus. The X-ray films showed the prepyloric region and the duodenum in spasm. Nevertheless, under the fluoroscope the duodenum was well outlined and appeared to be normal, but the prepyloric region appeared to be defective and was quite tender to palpation. Here again, the gastro-photor pictures showed the presence of an ulcer on the lesser curvature near the pylorus probably in the process of healing, Figs. 9, 9A.

The remaining cases were all negative for ulcer both on X-ray examination and the gastro-photor pictures. Four of these showed hypertrophied mucosa on the gastro-photor pictures, Fig. 10. The final clinical diagnosis was chronic gastritis in one and chronic cholecystitis in the others. Among the remaining cases we diagnosed one as lead colic, another as a retro-peritoneal lympho-sarcoma. The latter was con-

firmed by operation. The final interesting case was one of achylia of unknown origin. It is interesting to note that in these last three cases the gastro-photor pictures did not reveal any pathological changes in the gastric mucosa.

The number of cases reported is not large enough to give a complete demonstration of the value of the gastro-photor but enough evidence has been given to insure for it a place in the diagnostic armamentarium of the physician. Like all other means of diagnosis it is not infallible, and will not replace the X-ray or clinical evidence of gastric disease. There are, however, a large number of cases where the diagnosis cannot be made and only a gastro-photor picture will reveal the lesion.

My sincere thanks are due to Dr. Isidore A. Feder and Dr. George Ashe for their valuable assistance in this work.

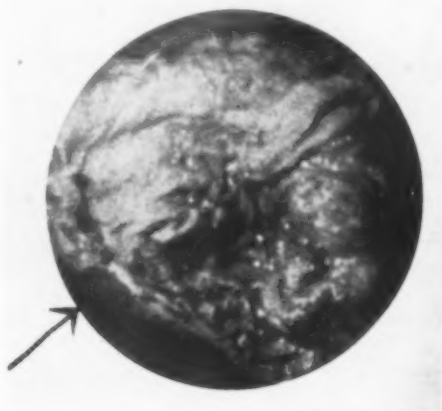


FIG. 5A. Case No. 38082; picture of pathological specimen showing ulcers in picture in Fig. 5.



FIG. 5B. Case No. 38082; X-ray of stomach showing no ulcers but which were found on post-mortem.

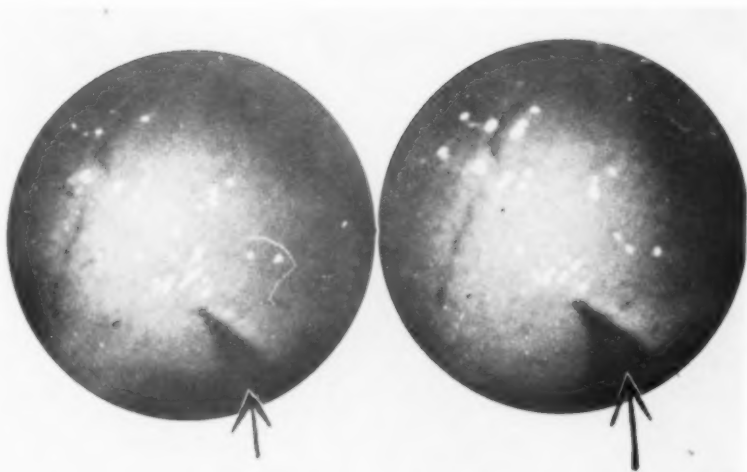


FIG. 6. Only spasm shown in case where X-ray shows a prepyloric ulcer.

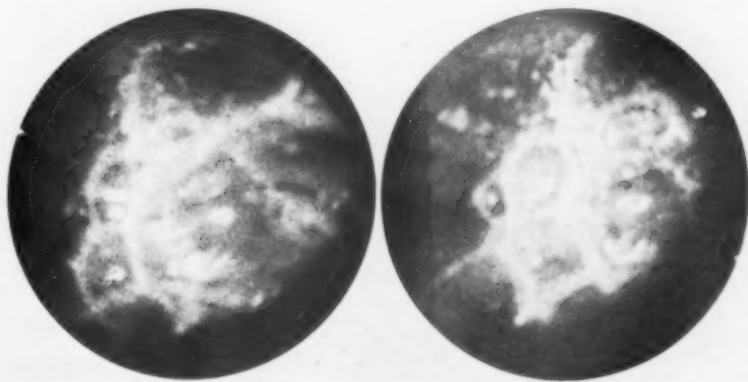


FIG. 7. X-ray diagnosis is gastric ulcer. Picture shows only hypertrophied rugae among which a small ulcer can easily be hidden.

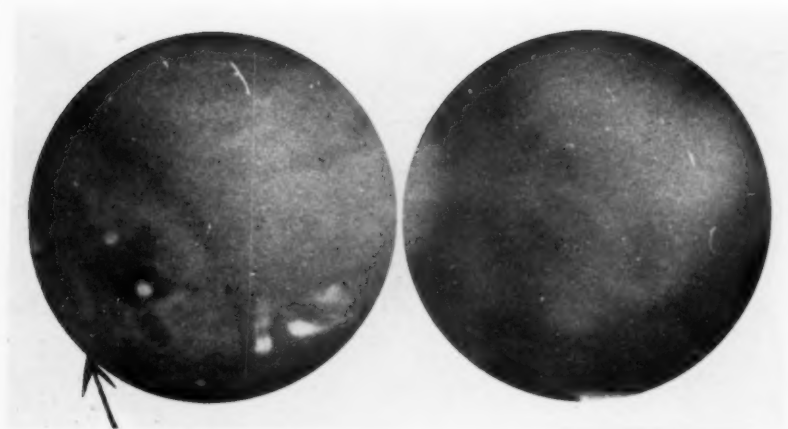


FIG. 8. At fluoroscopy there is some evidence of pathology at the pylorus. Picture shows an ulcer in this region.

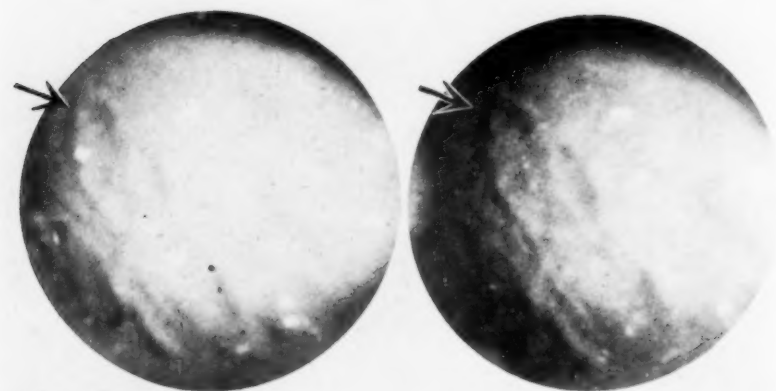


FIG. 9. The X-ray pictures are indefinite, the fluoroscopic examination shows a distortion in the prepyloric region. The Gastro-photor pictures show an ulcer near the pylorus on the lesser curvature.





FIG. 9A. X-ray of stomach showing spasm of prepyloric region. Gastro-photor picture Fig. 9 showed ulcer in this region.



FIG. 10. Example of hypertrophied mucosa in case of cholecystitis.

# Hereditary Juvenile Pellagra\*

## A Resume of the Literature

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### INTRODUCTION

PELLAGRA has at this writing vital problems, the nature of which still remains unsolved. In the last decade, exhaustive and intensive research, clinical, anatomo-pathologic, and experimental studies have added scientific interest to a disease known to Europe since 1735. It has, in a brief space of time, diffused itself throughout the greater part of the Old World and, as years passed on, was noted and described in many other countries.

The cause of the disease, the frequency with which it affects the infantile age, and the treatment, are topics most considered by the present day medical world. For a long time, one believed that it was a disease exclusively of the adult, forced to fatiguing field labor, exposed to the summer heat of the sun, nourished with scanty and improper food, when the more excessive the fatigue, the greater was the consumption of his forces. In order to find observations of pellagra in infancy and childhood,

it is necessary to go back to the works of the old writers, which have remained untranslated. One of our present day writers has well said: "If some of the early literature was modernized in language and expression and published in a journal of today, it would prove capital and stimulating reading to the most up-to-date student of the disease. Many of these early articles are characterized by a depth of comprehension, a wealth of assimilative experience, an accuracy of observation, an orderliness of arrangement, a well balanced judgment, and a breadth of scientific spirits which might be emulated by the modern medical man."

In the main, there is no attempt on my part to give to the profession original viewpoints other than that described in my first paper\*; or to take sides at this time regarding the etiology of pellagra. Personal references will be indicated and in the last paper of this series, a résumé of my findings will be discussed at length. These papers are the results of seven years of study. The translations were taken from many languages, especially from Italian, French, Spanish, Russian and German sources. There has been a rearrangement of thoughts, altered

\*This series of articles on Pellagra in Infants and Children was made possible through the munificent gift of Mr. and Mrs. Russell Clark, of New Orleans, in memory of their daughter, Alma Villere Clark.

translations and omission of all references not pertinent to infants and children. The writer's interest is predicated by the fact that the thorough knowledge of the cause of pellagra, of its peculiar manifestations in the young, is wanting in our literature. By the presentation of these papers, I trust that further study and experimentations will be stimulated; that a better understanding of the infantile type will necessitate an earlier diagnosis. Further than this—a completed bibliography is given to the profession. In conclusion, remember that the child is the father of man, that our efforts should be expended in limiting the mortality of children. If my efforts to present facts will aid the child in the slightest way, my compensation will then be complete.

#### *Heredity*

Still limited to some countries; not well known in its multiform clinical aspects; perhaps also less numerous and profound those somatic and psychic alterations which characterize the heredo—pellagrin, and demonstrate degeneration consequent on the slow and progressive toxic process; while the strangest and most diverse hypotheses regarding its etiology reigned, is it not strange or unusual that the infantile form was accepted with but slight consideration or denied entirely?

With the multiplication of the observations, of the works on the subjects; with the perfecting of the means of investigations, and of our knowledge on the general pathogenesis of diseases, and in particular of pellagra, it has not been difficult to discover that the disease is found also in the infant,

under manifold aspects, even if not with the same frequency as in the adult; and clinical forms, well characterized and distinct, have been studied. But specially there has been ascertained with clinical and experimental investigations, the injurious blastophthoric effect which the pellagra of the parents transmits to the product of conception, on a par with alcoholism, with syphilis, with malaria, and with other toxic and infective agents.

Pellagra is one of those diseases whose etiology is not yet perfectly known. Hence, the study of its epidemiology assumes an extraordinary importance, since it is known how from the exact knowledge of the epidemiologic phenomena one can many times, at least exclude with certainty some groups of etiologic factors. It is not necessary to call to mind of how many diseases it has been possible to affirm the infective nature on the basis of the demonstration of certain epidemiologic characters. Inversely, the lack of specific phenomena, in the study of the epidemiology, can be a sufficient criterion to negative special etiologic hypotheses.

In the recording of those authorities who accept on the one hand, and reject on the other the question of hereditary pellagra, one is impressed by the numerous Italian references. Unquestionably, the physicians and scientists of Italy, through generations, have had a better opportunity to observe this disease in all of its forms than any other country of Europe.

The classic signs and symptoms, other than those mentioned casually, or described in the translations of

*Gemma*, will be reviewed in detail in another contribution.

Infants who develop pellagra; children developing stigmata of degeneration in a short interim of time after birth; those who succumb to marasmus, malnutrition and inanition where these entities can be traced to pellagra, and lastly, individuals born of pellagrous parents, who perhaps do not develop infantile pellagra, but in later life exhibit classical symptoms of pellagra, will all be discussed in due time.

The transmission of pellagra by heredity was suspected a long time ago by *Odoardi* (1776) and by *Albera* (1781-1806). This belief was held also by *Strambio* (1786-1794), who could establish that up to that time the largest part of the pellagrins are born of pellagrins; that the offspring of these even in youngest age are more easily seized by the disease, that in the various families it is with difficulty that one finds an isolated case of pellagra, but several blood-relations (consanguine) are attacked together. ". . . As to age, I have already published many histories of pellagrous children, not only under 12 years of age, but 6, 4, 2 or even sucklings." He also mentions that among 126 pellagrins he found 15 individuals at the age of 1 to 25 years, wherefrom of course one can draw no conclusions specially as to child-age.

*Strambio* speaks of a man born from a pellagrous mother, who in his turn has had a daughter pellagrous even from infancy, and this one a baby boy with a nasty cutaneous affection. But his contemporaries have seemed little inclined to admit an influence of

pellagra on the descendants and in these the hereditary predisposition.

Later *Fantonetti* (1830) narrated that he had "seen a baby boy at the age of one year, who by the desquamation of the neck and of the hands even to the middle of the forearm one would have had foundation for calling him pellagrous. He was born of pellagrous parents, and had been carried around and also held in the sun; hence it is not in any way contrary to reason that in some cases it can happen that from pellagrous parents may issue a child with organic conditions which may bring it also to suffer from pellagra." And farther on he has added: "It seems very well that pellagrous parents can give origin to children, who will easily fall into pellagra, particularly as they may remain in the same conditions of food, of shelter, of work as the parents.

Concerning the influence of inheritance *Roussel* (1842) speaks in manner worthy of the highest consideration. He distinguishes three sorts of hereditary factors. The *first* sort includes those diseases which originate in the parents and find continuation in the infantile organism: those are the *morbi connutriti* of the ancients, the *morbi parentales*, as syphilis or variola. The latter disease, undergone by the fetus, gives to this and to the following child immunity. In this sense pellagra may not be hereditary.

The *second* sort included diseases, whose germs are instilled during the development of the forthcoming being. These germs are at first not manifest, the child seems healthy, and only with the development of the child did they come to maturity and lead to devasta-

tion. As example he alleges the inheritance of scrofula, of cancer, and of other cachexias. Of course, to our present day view these examples no longer correspond. *Roussel* does not reckon pellagra among this sort of congenital diseases.

Under the *third* sort he understands now the simple similarity of the infantile organism to the parental, which lets the growing one seem less "resistant" against like detriments. Here he reckons pellagra, and in this sense he grants an inheritance in case of this disease, but not the inheritance of this disease. Today we would say, in case of pellagra heredity is the "predisposing" cause (constitutional or predispositional inheritance). But then such "hereditary" pellagra may not have a special clinical form.

*Ghiotti and Longhi* (1844) conclude, in their investigations, that of the 1,319 persons examined, who were descendants of 184 pellagrous families, 671 were healthy, and 648 were pellagrous. Their study deduces two very interesting conclusions: (a) a tendency for the affection to be more commonly transmitted by parents to children of their own sex and (b) that the malady is more often inherited from the mother than from the father.

*Calderini* (1846), in a recapitulation of 96 couples where both parents were pellagrous, noted that there were 116 sons and 106 daughters pellagrous; in 160 couples where the father was pellagrous and the mother was healthy there were 64 sons and 49 daughters. In another series of 175 couples, where the mother was pella-

grous and the father was healthy, 30 sons and 38 daughters, born of this union, had developed the disease. In addition, he offered some very interesting data regarding hereditary pellagra. In the 1,005 patients admitted to the City Hospital of Milan, 1844-46, 300 of this number developed the disease before the end of the third year—one-fifth of this number was male, and one-fourth female. Later on he refers to 352 pellagra cases, of which 83 were under 3 years and 15 between 3 and 12 years. Indeed the tenderest infancy may even be the selected age.

The Piedmont Commission in 1847 closed its report affirming that for the most part one is born pellagrous, exaggerating thus the truth of the clinical postulate.

*Lussana and Frua* (1856) state that "the pellagra of infants appertains to individual children of pellagrous parents," and note again that in the children "the pellagra is mild because in the first stage."

*Gemma* (1871) as the most noted and criticized exponent of hereditary pellagra has said:

"This is a fact quite painful for the man of natural science, this being obliged to go again so many times over the same road, finding on the way the obliterated footprints of his predecessors. In this manner at every step arises an obstacle to progress, and the near horizon of truth removes itself by degrees as we advance in our studies. And this fact is so much more painful, because it happens more often not by the discovery of scientific materials new and contradictory, but because the man makes himself slave



of his theory and humiliates the expression of the facts to his own idea. This has happened also in admitting hereditary pellagra."

"*Roussel* had already at his disposition an archive of histories, and the confession of distinguished pellagrolologists; he possessed the fruits of his scientific travels in Italy and Spain, he could place in combination the statistics of *Lussana* and *Frua*, demonstrating that the etiologic element of one-third of the pellagrins of the great Hospital of Milano was heredity, the statistics of *C. Gallo* and of *Calderini* demonstrating that the disease had begun under 3 years, in 300 individuals. Instead he terminates with saying, 'qu'il n'est pas vrai qu'on naisse pellagreu; qu'il n'est pas vrai qu'un germe pellagreu se transmette par l'heredite.'

"How he has arrived at this conclusion, through a series of contradictions, it is useless to recall. After having admitted in one page that 'l'heredite est un fait aussi unanimement reconnu,' in the following page he writes: 'Lors qu'on a etudie de tres-pres les familles pellagruces, on est amene a ne pas faire consister le fait de l'heredite dans la reproduction de la pellagre proprement dite, et tout entier chez descendants des pellagreu.'"

"It is convenient to say that he has been fully convinced that the fact of heredity was an insuperable barrier, was the wall of China against which must of necessity beat to pieces the arms of the defenders of the maidic poisoning, if one set himself to fight it with effort, and with a power of talent worthy of better cause."

"And in what manner could he combat a fact unanimously recognized? To feign to be ignorant of the facts for a pellagra encyclopedist, such as is *Roussel*, was impossible. To deny them would have been indecorous boldness. Then? Then it was convenient to deny them, facts the most explicit, the most fearful; those which could be attacked in one way or in another to confess them, giving to them a different interpretation. In short to stay on horseback, to form a neutral ground, on which one could be comfortable at his own beautiful ease. This he has done in fact, and one cannot deny that he has done it with much self-possession and courage, if not dexterity.

"Therefore one inherits pellagra, no one today contests the reality of it, but it is a metaphor, but it is not properly pellagra and all entire pellagra; that is, one inherits and one does not inherit, because that which seems pellagra is not pellagra, although the pellagrolologists may call it pellagra; in short I do not know how to express myself, but *Roussel* has understood all.

"He commences with denying that some cases were pellagra. In the history of pellagra he asks, has one imagined facts of an appearance analogous (to the parental diseases), I speak of those unlucky newborn ones or sucklings, who have offered all the symptoms of confirmed pellagra? The cases of *Zecchinelli* specially, it would seem that they ought to be related to case of pemphigus of the newborn (disease which would itself be frequently a syphilitic disease). As for *Strambio* (note well *Strambio*), who

has said that the greatest part of pellagrins owe their disease to pellagrous parents, he believes it opportune to correct him by substituting for greatest part (*la maggior parte*), beaucoup.

"He reports the beautiful description of *Sacchi* (reference and date not found) on the hereditary influence, description which I wish to reproduce today."

"It happens to me sometimes to observe little creatures with all the indications of a perverted vegetation. I cast a glance at their parents, and withdraw my looks shuddering. This little being will remain vitiated for all the course of its life, which will not be long, or if he shall seem to develop himself a moment, that will be to plunge down again later under the influence of the causes, which will alter more and more his organization already altered. It is a common custom in our country districts,—speaking of a person who suffers of ills long and unknown, in the most beautiful years of youth and of virility,—to say that he has inherited his ills; and the ills are no other thing than pellagra. There is then a particular or pellagrous habit; a good long time before the development of the pellagra, one can recognize the individual who will be attacked, by his vacillating and uncertain step, by his eyes with a yellowish reflex, by his fixed stare, by the color of his face pallid or yellowish, by the tarsi of his reddish eyelids, by his cracked lips, by his scanty hair . . . by his forehead furrowed with wrinkles beyond his age, by his soft musculature, in short by his suffering and apathetic aspect." . .

"Well then! To the energetic picture which manifests the observing mind of our Italian, and which today merits several additions, what does *Roussel* respond? . . . Whether there are exaggerated features in this picture. . .

"But to the detailed observations of *Lussana* which demonstrated heredity to *Lussana*, how does he respond? They are adults who have lived in the pellagrogenic conditions, that is, have eaten infested polenta and who for that reason have become pellagrins.

"And it goes very well. I have heard that a bizarre brain takes it into his head to demonstrate with historical and philosophical arguments, that Napoleon I has never existed. As for me today I shall believe in him. But then what is science? A stage, and we are the actors who await the applause and the hisses of the cultured public, according as we represent well or badly our part.

"In the same manner that *Roussel* and companions deny the heredity in the strict sense of pellagra, I would be able to deny the heredity of rachitis, of scrofula, of arthritis, of cancer, and even of syphilis.

"But *Roussel* himself cannot deny that there exists something hereditary. Well then; this something is the pellagrous substratum (*fondo pellagroso*). 'Il n'est pas vrai qu'il (*Sacchi*) peint une realite, a laquelle il a fallu un nom particulier et pour laquelle on a cree l'expression encore si mal definie de fond pellagreux.' Behold then the grand discovery. The children of pellagrins are—as he says—of a sad aspect, cacochemic, of lean tint, of downcast air, but nothing more; these are not pellagrins, but they have the

pellagrous substratum, and become pellagrins when they have been subjected to the use of polenta. Hence there does not exist the weak fomite, the pellagrous germ of *Lussana*, the substratum exists. For pellagra one cannot use the expression *heredity*, which represents a true cognition, which signifies a fact which we see all the days, and one as ancient as reproduction itself, which if not yet explained, remains and will remain always an acquisition of science; one must use a new expression, created for the purpose, and so defined badly.

"No; with the means of the terms, with the subterfuges, with the substitution of words the sciences are not created; not in such manner are erected edifices which can resist the impact of the centuries; one erects on the sand and the first breath of wind will scatter the fruit of our labors.

"*Roussel*—was he then competent to judge of such a question? See the answer by himself: 'la pellagre a chez nous un champ plus limité qu'en Italie; elle y est moins grave, et les influences de l'heredité y sont moins manifestes.' He then who judges *Strambio* and *Lussana* is a man who lives in countries where the pellagra has less hereditary influence.

"We are not ignorant of the travels of *Roussel* in Italy, and specially in Brescia, a province extraordinarily infected by such disease. But is it possible to see all the phases of a disease of the people so protean, or of a constitutional stain, seeing it for a few days? Who will be more competent, the one who judges it in such manner, or the one who has lived long years

among the destructions of pellagra, observing the vicissitudes of it?

"And here is necessary a justification. I have taken aim at *Roussel* for his ideas on pellagrous heredity, because, as one may say, he understands all the reasons which seem to oppose themselves to this fact. I never combat the man, but the idea. For that matter, I have the greatest respect for *Roussel*, as scientist and pellagrologist. If he, dominated by a preconceived idea, which without the outfit of sufficient proofs, presented itself to him as fascinating, because according to him it must of necessity form the basis of the etiology, of the pathology, of the prophylaxis, and therapy of pellagra, if he, I say, fell into some error, what wonder? I appreciate very much his work, I have studied it profoundly; it is certainly a monument of glory for its author, if it were only as a well ordered pellagrologic encyclopedia.

"After *Roussel* has come the work of *Lombroso*. He has admitted, with brief description, pellagra with imperfect development and mild hereditary pellagra. But the opposers would be able to reply that the first is not pellagra, but an organic alteration which can develop in the children of all the deteriorated organisms; the second is not hereditary, but dependent on equal dietetic conditions. On all one can cavil.

"In what manner to render demonstrated as fact which is already universally admitted? With statistics? The opposers would not have lent faith; were there not statistics already? With clinical observations? It is always the best means, but it was suitable to use it with the greatest pre-

cision; since if there had been found a single pretext, such and such a subterfuge, they would have responded the usual ritornelle of the common hygienic conditions, or else of the mistaken diagnosis. The maidists all pretend to a particular prerogative, that is, not to be able to diagnose and know any pellagra but theirs. They are like the priests of all the religions, who declare impious all those who do not think as they do, and devoutly they curse among themselves. What pleasing minds! . . .

"Up to the present time this subject has been rather deflowered than studied; one has established as a fact, that is, that even infants (*bambini*) can be subject to pellagra, and that in them it depends on heredity in the maternal line, but that solely in etiologic scope, without seeking to eviscerate this important point of the pellagrogenic pathology.

"Let it not be believed that here I wish to occupy myself with the etiology of pellagra in general. I ought to establish as a fact merely that the chief cause of the pellagra of infants is *heredity*, a thing—to tell the truth—observed by others.

"For the rest the imprint of heredity extends itself still farther, and while the parents, who suffer from neuro-muscular pellagra, but are in sufficient state of health and of constitution still quite good, usually give children well developed, those who suffer from atrophic pellagra, give children also in this condition.

"The process of dentition does not seem to have in pellagrous children a greater influence than that which it has in other infants, children of

healthiest parents. In all the cases observed by us, and diagnosed as pellagra of infants there was no work of inchoate dentition (*dentizione inchoata*—that is, begun but not finished). On the contrary, the gravest case and the one which has terminated with death, was, at the age of 2 years, provided for some months with all his teeth, which had developed themselves without any inconvenience, while the pellagric phenomena have manifested themselves in him with the beginning of the summer.

"A singular fact, and which certainly will be evident to the attention of our readers is this: *that one inherits the special pellagrous form*. To *Lusana* is due the merit of having introduced the most practical division of the pellagric forms. The present studies on heredity, while they come to confirm such division, demonstrate this new fact in our game, that one can inherit the form. It goes without saying that this fact ought not to be accepted in the sense of a mathematical precision. In the sciences of observation and specially in pathology, it is difficult that that should happen. Thus, for example, if a father has had cerebral pellagra, and the son also has had such, in this last one could be associated some intestinal phenomena, but the cerebral phenomena, however, will be the most salient. That which constitutes the fact under discussion is this, that the parents affected by cerebral pellagra give almost always cerebral pellagras in their children. The same goes said for the dermo-intestinal, for the neuro-muscular, and others. This fact is certainly an important acquisition, because it demon-

strates that not only is such a disease hereditary, (ereditario) like all the other hereditary (gentilizii) diseases, but is more manifestly hereditary than scrofula and than tuberculosis.

"And now, how can one say that pellagra is not inherited all complete? Perhaps because in many individuals it manifests itself when they have reached a certain age? First of all, who is there who can assure us that those individuals have not manifested the pellagrous phenomena in their first youth? In order to exclude this supposition, it would be necessary that a physician should have observed them for a long series of years, that which cannot be done, except by one who has practiced medicine for 30 or 40 years in one same locality. But even admitted that the individual, first was healthy and had all at once in adult age manifested the pellagrous phenomena, what can one infer from it? Even tuberculosis, to which no one denies heredity, develops itself in the greatest number of cases in youth and in adult age; rachitis on the contrary develops itself in infants and in children; scrofula and syphilis in infants, children and adults; cancer in late virility. Pellagra, developing itself hereditary in every age, would resemble scrofula and syphilis.

"That the hereditary pellagra cannot be explained with the co-existence of the same hygienic and domestic conditions, let us believe results sufficiently illuminated, not only from the pellagra of the newborn, but also by the accompanying case histories. We have seen that this manifests itself, not only in the peasants, but in the well-to-do of the country, in the poor suburbanites,

and even in the rich citizens, when the germ exists in the family. The hygienic conditions, however good, are not sufficient to exorcise entirely pellagra, when it exists in one's own genealogy. And the number of well-to-do of the country who suffer the disease is quite other than small; I could bring forward a quite larger quantity of cases, if I had not determined some limits for myself.

"And now we make a comparison between this heredity so certain, so evident, which so much resembles that of scrofula, with the heredities of mercurialism; 'and in general,' writes *Lombroso* (*Sull'etiologia della pellagra: riposta ad alcune obbiezioni*) 'the female workers in mercury bear children scrofulous, rachitic, tabetic, and affected by grave cutaneous diseases.' And this, to speak truly, is quite a strange manner of understanding pathologic heredity. I shall be able to demonstrate, and I will demonstrate it in what follows with the facts, that from pellagrins can be born children, scrofulous, rachitic, tabetic, oligocythemmic, but with that I will never say that those scrofulous ones, nor those rachitic or tabetic ones have inherited pellagra. I will say only that the children have inherited pellagra, when they shall be pellagrous as the parents have been. It is natural that unhealthy fathers give unhealthy children, but this fact is not sufficient to constitute pathologic heredity. I see in general, that old parents give life to delicate children; does one then inherit old age? These examples go absolutely refuted as hereditary diseases, when one does not wish to affirm that scrofula and rachitis are the same



thing as mercurialism. But there are cases more explicit: 'Mayr (loc. cit) has noted three babies of workers, who on the 14th day from the birth, presented the mercurial tremor; on one (male) it has presented itself the very day of parturition, in a girl after a year with stomatitis and ptyalism. Another girl born while the mother—very rich and well nourished—was a prey to mercurialism, has presented smallness in the person, salivation, lack of teeth; the other children born after the mother was cured of mercurialism, were very healthy.' Behold another history taken from *Russmaul*: 'Laborer, who 12 years previous has had to suffer by effect of his profession, mercurial salivation, loss of teeth, was married three times: the four children of the first wife, who was a worker in mercury, all sickly have died, three of consumption, one of gangrene of the feet, and so also the two children of the second wife. Of the third wife, the children born while she was working in mercury, have died; the others placed in the world after the mother ceased from the work, have survived.'

"These facts I believe have no need of criticism; these, if one believes thus, may also be called hereditary, but it is certain that then it is fitting to trace a great line of demarcation among the pathologic heredities. These cases near to the birth, can be considered as a continuation of the paternal poison, or maternal, and to be counted among the diseases which are called congenital, rather than hereditary. The single case farther from the birth is a girl of one year. She has had stomatitis and ptyalism, which

could originate in other causes. But we are not accustomed to contest the diagnoses of the adversaries. It is necessary that we establish the enormous diversities which pass between this and pellagrous heredity. The adversaries of heredity, supporters of poisoning, reproached us, years back, that there were no cases of pellagra, well assured, near to the birth. We have presented them, and we have presented also some of them quite distant from birth; now in our turn we can say: present to us cases of poisoning distance from the birth, which have the characteristics of hereditariness.

"Likewise a mother affected by smallpox can bring forth a child with smallpox, but no one will wish to compare this fact to scrofulous heredity. A mother infected with syphilis can bring forth a syphilitic; but what difference, if instead the mother, being healthy and having suffered formerly of syphilis, brings forth a child in whom later is developed syphilitic lues? The first case would be congenital, or contagious; the second hereditary.

"In the sense generally adopted (I take the definition from *Roussel*) one understands by heredity, not the disease itself of the parents transmitted to the infant in all its development, but a principle, or if one wishes, a germ detached from the parents, whose development does not take place except with the development of the organism.

"It is in such manner that is hereditary—scrofula, rachitis, cancer, the tuberculosis; and in such manner is hereditary also pellagra. A child of tuberculous persons can attain in health, for example, to 20 years, and



in that age become tuberculous. Before that age, the most advanced ascultator will find sometimes a perverted constitution, but nothing which can make him pronounce the diagnosis of tuberculosis. A child of cancerous persons can become cancerous at 40 years; but before that epoch the wisest clinician would not find the signs of the disease. Later, perhaps, the progress of the microscope and of animal chemistry, will explain to us these unknown things; but until that day it is fitting that the medical practitioners respect the facts, if they do not wish to walk in chaos.

"The same is repeated in the comparison which one wished to make between the heredity of alcoholism and that of pellagra. The hereditary ones of alcoholism of *Burdet* are thin, cacochemic, poor in spirit, often idiots, subject to scrofula and above all to convulsions and to the cerebral maladies (*De l'ivrognerie et de ses effets*). The cases of *Guislain* are insane; the 16 cases of *Marce*, son of an alcoholic, have all died before 3 years of cerebral accidents, except an epileptic. And these are all hereditary alcoholists; hereditary like the tuberculous, like cancer? What ought one to reply? That the spirit of partisanship blinds, even to delirium, also the men the most profound in science. Well then; from now on, if a son of a tobacco smoker shall suffer of pneumonitis, we shall say that that is hereditary pneumonitis by reason of nicotinism.

"Yes, also from pellagrins can be originated children sad, unhealthy, cacochemic; also in the children of pellagrins there is a frightful mortality; also in our histories every one can

observe this fatal hecatomb of young lives. But these cases are not pellagrous heredity. These must rather form part of an interesting study, which would be that of the transformation of the hereditary diseases. *Roussel* has said that 'the families in which exists the pellagrous substratum are extinguished and disappear easily under the blows of different occasional causes, with which pellagra has nothing to do.' We also have spoken of these facts, and we will bring others subsequently, but let us not fear that these may weaken pellagrous heredity.

"We ought then to conclude that the manner with which one inherits pellagra is quite different from that with which are inherited the known poisonings. And also here, as in other facts, the pellagrolologic clinic and pathology stand against the theory of the poisoning. Besides, if the heredity of this disease presents itself under five forms, it would be fitting with such theory to admit that the poison of the maize had five manners of acting, or that in this cereal existed five poisons, each of which was partial to an organic system, dwelling in this even to the third generation.

"And now what is the mild hereditary pellagra of *Lombroso*? It is a hereditary neuro-muscular pellagra. Whoever then considers that not always—it is true—does one die of this form, but that still it torments sometimes the entire existence of an unhappy one, that the onset or rhythm having developed itself, this lasts sometimes several months, that it is necessary often to use all the known reconstituents, to use energetic reparatory therapy on the nervous system;

and that with all that the patient is not profited—sometimes—except with the return of the autumnal season, this one will not know how to understand in what such 'mildness' consists.

"After these proofs and those adopted in the pellagra of sucklings and of newborn, we ought to conclude that pellagra is a *hereditary disease*. With that it is quite natural that one does not deny the acquired or primitive pellagra. The two facts not only can, but they must necessarily both exist; because to become hereditary, it is requisite that a disease introduce itself in some individual of the family. In other words, pellagra goes frankly compared to all the hereditary (genitilizzi, family) diseases.

"We have victoriously repelled all the objections which have been made on the subject. One has said that the pellagrous infants did not exist, and I have demonstrated that pellagra is developed in sucklings; one has said that that of infants was not pellagra, but cacochemic delicateness, and I have found infants with erythema. One has said that many pellagras of the authors could be interpreted differently, and I have presented some of them so detailed and circumstantiated as not to be able to leave any doubt; one has said that the appearance of heredity depended on the influence of the same pellagro-genic cause; but I have demonstrated that, even changing the hygienic conditions of a family, one can develop pellagra when it exists in the same.

"But in order to demonstrate, that the pellagrous heredity is a heredity, like that of other hereditary (genitilizzi) diseases, and not a substratum

of depauperization, on which the pellagro-genic cause determines the pellagra, we have in hand organic proofs which certainly have escaped *Roussel*. These proofs result from the constitution itself of the pellagrins. We desist here from speaking of the pellagra of imperfect development, which too clearly presents its characteristics; also the common hereditary pellagra can be quite well known objectively."

*Bassi* (1880) apparently had not specialized in the particular disease he now discusses, but states, nevertheless, that "while it is generally declared that pellagra is not contagious, one wishes nevertheless to call it hereditary. That does not seem to me as yet legally proved.

"In order to assure ourselves of it, to doubt it no more, it would be suitable to take some babies (*bambini*), and repeatedly, in order better to assure one's self of the truth, some babies just born of pellagrous parents, and brought soon into families in which individuals do not nourish themselves at all with maize, or if they feed themselves with this, they use it in the healthy manner referred to above by me; and here nursed by nurses who will feed, or feed themselves in the same manner; and kept here in the midst of the same families up to the adult age, living and exercising themselves in the manner of the persons composing the families themselves, which (the families) in order better to ascertain the truth—it would be well that some should be dedicated to field labors and others to various factory labors; and it stands then to see whether there manifests itself in one

or the other age in these children of pellagrins the pellagra which afflicted their parents; and, manifesting itself in this case alone, one will be able to say legally that pellagra is hereditary."

*Lombroso* (1885), speaking of pellagrous heredity, divides it into two species, the one very grave, the other mild. From what he writes, it is easy to convince one's self that his exact observations are directed to mark the characteristics which distinguish the hereditary pellagra from the acquired in the adults, rather than to study the pellagra of infants. In other words, he establishes that which one would call the *habitus* of the pellagra. In regard to the gravest hereditary pellagra, he writes that "it manifests itself from the second year of life, rarely with desquamation, more often with pains in the epigastrium, pyrosis, voracity, uncertain walking, easy fear, diarrhea, yellowish aspect as in the fevers of malaria, and retardation in the development."

*Sepelli* and *Lui* (1899) explained their interpretation of heredity as a "transmitted degenerative condition in which, as may be the case with alcoholism and certain chronic intoxications, there occurs essential modifications in metabolism and in the functioning power of the nervous system, determining in the descendants of pellagrins a weak constitution, and producing a state of lowered resistance, which leaves the individual especially susceptible to the maize toxins.

"Well then, in 173 insane pellagrins we encountered pellagrous heredity, now direct (95 times), now indirect (6 times); or that is, in the enormous

proportion of 58.3 per cent. Further, we encountered pellagrous heredity not rarely in forms plainly degenerative, such as phrenasthenia and epilepsy. Taking then into examination in our patients of mind those morphologic anomalies which have a value more or less accentuatedly degenerative, we made note how the insane pellagrins offered us a considerable percentage of degenerative signs, principally in such respects as the cranial malformations and those of the face, the pathologic expressions of goitre and of rachitis."

Their findings have been substantiated by *Bonservisi* (1899), in his accurate statistics of the Mantovan pellagrins, established that, out of 2,718 children of pellagrins, 1,093 were dead under 5 years, about 160 in the following (years), and the others living presented degenerative marks, gastro-intestinal disturbances, or true forms of pellagra. Of the 1,460 living, 59 had habitual intestinal disturbances, 81 were true pellagrins, and 311 weak and sickly. Hence, while in healthy families there was under 5 years, 290 per mille of mortality, in the families of pellagrins it was 402 per mille, almost double.

"*Antonini* (1902) has found in man a confirmation of the experimental pellagrous teratogenesis of *Ceni*. Examining the degenerative characteristics of 59 hereditary pellagrins, he found them 38 times, that is in 62 per cent, while in 98 pellagrins *not hereditary*, he established them as a fact only in 18, or that is in 17.9 per cent, which demonstrates how children of pellagrins become subjected to ar-

rests of development and to deviations with a frequency by far greater than those who originate in families immune from pellagra.

"*Conclusions:* 'There exists a pellagrous heredity confirmed also by experimental researches demonstrating how the nutrition with spoiled maize diminishes the procreative power and favors the development of teratological products.

"It is interesting to examine the composition of the single families divided by communities. Hence, I set forth the tables which are the result of the spoils of the tabulations returned by the sanitary officers with the indications. For brevity I limit to the first hundred of families, certain that no modification of the conclusions will be able to be brought by the pursuing of the inquiry, because these first hundred families belong to communities of all the commissions without any selection.

"We have, therefore, that one hundred *non-pellagrous* families have given 616 sons, of whom 200 have died, and 416 are living at the moment of the inquiry.

"Hence the proportion between the sons dead and the living is that of 48.07 per cent.

"There have been born dead seven, and aborted nineteen.

"In the 100 pellagrous families, on the other hand, there have been 523 sons, of whom 225 have died and only 298 were living at the moment of the inquiry.

"The proportion, therefore, between the sons dead and the living is that of 75.5 per cent.

"There have been fifteen born dead and thirty-two abortions. Thus it remains confirmed from this numerous statistics that pellagra diminished also in man the generative potentiality, and that in the sons of pellagrins there is a mortality of a good third above that which is verified in the families of normal persons in the respective communities, and precisely in a proportion of 100 to 159. That is, if in a certain number of normal families 100 sons die, in the same number of pellagrous families 159 of them die."

*Influence of the Blood of Pellagrins on the Product of Conception*

The subject was the object of experimental researches by Professor Ceni (1905) himself, of the Istituto Psichiatrico of Reggio Emilia, who first of all has established that the blood of pellagrins in general, and in especial manner of those affected by actue forms, was constantly presenting physio-pathologic modifications, in direct relationship with the toxic agent and with the lesions determined by this in the organism, modifications which are endowed with teratogenic power much superior to that of the blood of healthy individuals, and capable of having an influence on the development of the product of conception: the experiments have been done with the method of intra-albuminous injections into the eggs of the hen.

With a new series of experimental researches he studied also the direct influence which pellagra exerts on the procreative power, using hens as experimental animals, slowly intoxicated with feeding of spoiled maize, and saw that the power of proliferation not

only in regard to its duration, but also in regard to the number of the products of generation, was reduced; that such nutrition brings modifications to the ovum and to the spermatozoon before their union, which modifications manifest themselves subsequently in the abnormal evolution of the embryo: this (abnormal evolution) then consists in a congenital exhaustion more or less accentuated and precocious of the vitality of the product, and hence in a general retardation in its evolution, or in early death, and in the gravest cases in partial death of the germ, only the blastoderm developing itself, and even in total death, in which case is included also this last. The anomalies, hereditary in the true sense of the word, consisted in partial arrests, and sometimes total ones of the primitive vesicle of the cephalic extremity (anencephalia) with enormous development of the ocular ones (macrophthalmia), in punctiform hemorrhages localized specially in the cephalic extremity of the germ, this fact being united (a) to an abnormal state of all the primitive circulatory apparatus, (b) to a greater fragility of the walls of the vessels, or at least (c) to a disproportion between the blood-pressure, and the resistance of the walls themselves: the vessels in fact presented ectasiae, varicosities with hemorrhages and extravasations of various degree. Under multiform aspects this is an important fact—the frequency with which the anomalies of development, the monstrosities were related to the cephalic extremity, deviating the evolution of the primitive central nervous system. By reason of all this, it remains demonstrated that

the maldic poisons, which circulate in the organism of the parents, specially of the pregnant one (gestante), are capable of determining (a) a precocious state of exhaustion of the product of conception, which explains to us the frequency of the interruption of the pregnancy, and of the death of the fetus; and (b) again grave deviations from the typical form of embryonic evolution, giving anomalies, important monstrosities which we encounter frequently even in man; and (c) finally, that that predilection, which the toxic element shows for the central nervous system after birth, is observed also on the primitive elements of this, whereby the *pathogenesis* of certain congenital nervous forms, such as spastic paralysis, hydrocephalus, meningitis, encephalitis, microcephalus, etc., which present themselves in heredo-pellagrins, receives thus exhaustive explanation.

But in addition to these facts, which can be established with our means of investigation, other anomalies and alterations will certainly take place, which it has not yet been given to us to know in their intimate nature by reason of the insufficiency of our studies, and of the means at our disposal, which (other anomalies and alterations) will determine the organic predisposition, the receptivity to morbid forms, general and special, systemic, localized, in infancy or in the adult, according to the intensity with which they acted and modifications which they brought into the organs and into the systems.

*Simonini* (1905) admitted that the maternal maldic intoxication has af-



fected the foetus, giving arrest of development of the nervous centers and perhaps also determining the lesions of the cerebral and spinal meninges.

Discussing heredity, he asks "in what consists this hereditary predisposition, so difficult to define?"

"(a) From the one side one can conceive it as an arrest, an evolutive regression of a tissue, of organs, and of a whole system, which for this reason are more susceptible to new morbid stimuli, and less fit to react; (b) on the other hand this (hereditary predisposition) is certainly connected with toxic and infective processes.

"In a general way, one can consider demonstrated that these processes of infection and of intoxication in the parents, especially in the mother during the period of the gestation, are cause of retardation of the development of some tissues, and sometimes also of arrest and of various alterations which, although cured, appear in relation with morbid forms, which are verified in the extra-uterine life, as happens for some degenerative neuropathies. Nor can pellagra be withdrawn from these general laws, whether it depends on an infective or a toxic process; and hence it is necessary to admit the predisposition, the heredity, the degeneration, which induces in the descendants who are born with the easiest tendency to fall sick of the same affection, and of those pellagrous forms, which the parents themselves had manifested."

*Alpago-Novello* (1905), in his thirty-six years of experience, has recorded only two nurslings, who received breast milk, complemented with maize,

where a diagnosis of pellagra was clear.

*Merk* (1909) states as follows: "If I summarize all these statements of *Gemma's*, then I regret only too keenly—and I hope the majority of the readers are with us—the effort for exactness corresponding only half way to his zeal for the subject. In the year 1871 one must already have had fever-curves, or at least degree-statements, body-weight-determinations, number of the pulse, of the respiration; more exact communications concerning the nourishment and similar matters can be expected. One dare not forget that the treatise gains significance through the circumstance, that the journal, in which it is published, was edited by one *Gaetano Strambio*, a name which through two generations has played an eminent rôle among the pellagrolologists of the Lombards. The multitude of physicians, who consider science as something which has *become*, but never as something which is *becoming*, who work only with completed results, is led by such apodictic delineations to inexact diagnoses, and thereby suffers not only the study of this devastating disease, but also mankind itself, because the authorities, supported on the statements of such physicians, squander precautionary measures against pellagra, where no pellagra exists.

"When one thinks that *Gemma* set himself the task of delineating the pellagra of sucklings and of small children, that therewith according to his own words he wished to work out something new, then one must be astonished, that he has not given any word at all of the differential diagnosis



so important in case of such vague symptoms, that he has satisfied himself with saying: For me it is pellagra!

"A specially strong link in the chain of Gemma's proofs seems to lie in this, that the diarrheas and other symptoms of his "hereditary" pellagra were cured according to *Lombroso's* method on administering arsenic or quinin-arsenic.

"Gemma's blind confidence is the more surprising, as he does not trouble himself about the literature up to *Lombroso's* treatise and his own publications, although precisely then the question of heredity, as well as the question of pellagra in case of children was still discussed in lively manner. This is true among others also of his nearest countrymen in Milan.

"But from grounds of general natural history sort, I cannot myself decide as to the conception of such heredity of pellagra, and point out this, that kindred equal relationships, as life-manner, life-customs, climatic relationships, only too easily simulate heredity and hereditary tendency.

"Before I set myself to the epicrisis of this case so especially rich in suggestive and instructive details, it is still necessary, in order to suppress every doubt in what follows, to determine whether it has here been really a question of pellagra.

"If I had in the beginning relied on the authority of the above mentioned gentlemen best known to me, who have knowledge of my purpose to evaluate the case in the literature, I can now refer to the delineation of the case itself. It is, if one thinks that it is a question of ambulant material, positively exhaustive. Especially the skin

symptoms bear that striking characteristic, as—in case of this disease (particularly in the culminating state) for every one, who bestows on it only a half-way attentive look,—it is so extraordinarily marked.

"I refer again in summary to these symptoms: rapid onset; erythematous character, long extended course; sharp and outlining limit; hyperkeratosis; predilection-places, as face, back of hands and feet, gray-brown color. Besides come the juvantia of the diagnosis: additional pellagra-symptoms: the endemic; the maize-feeding.

"Further it is necessary to determine that the child was not sick of so-called "hereditary" pellagra, but of self-acquired pellagra.

"I am not in position to state exactly by whom the word—not to say the idea—"hereditary" pellagra was first used in this literature. I can only say that a hereditary pellagra has not been scientifically demonstrated. And farther: where always in the pellagra-literature the proof—not the assertion—of a hereditary form is sought so to be brought out, that one is in condition to lay thereon the measuring-rule of a criticism, it is easy for one to determine the incorrectness of this proof."

*Alessandrini* (1910) emphatically states "it has never been given to us to find pellagrous babies. With a limited number of patients, it has not been possible for us to establish whether heredity has had an influence on the development of the disease." However, in another paragraph I have found the statement "because in the same family where the components, more or less, must undergo the sad

consequences of unfavorable hereditary, hygienic and dietetic conditions and of excessive labor, only a very few members (one or two, rarely more) fall sick."

*Marie* (1910) believes that at times the disease is hereditary and that the children of generations of pellagrins are frequently feeble in resistance.

Though *Sambon* (1910) does not accept the disease as hereditary, he believes, however, and advances the idea that "the infant can contract the disease 3 to 11 months after its birth, a fact which he explains thus: the mother carries the infant with her to the fields at the time of agricultural labors, and it is there that *simulium reptans* inoculates into this last the morbid germ."

*Marie's* "Pellagra" (1912): "Most authors agree that the disease does not occur in infants unless they are fed on spoiled corn."

*Snyder* (1912) in accumulated data received in answer to letters addressed by him to sixty physicians who, for the most part, had had wide experience with pellagra in this country, summarizes the sixth question—Do you regard heredity as an etiologic factor? Why?—"Regarding heredity, all answers but six were negative. These six expressed the opinion that heredity should be considered, but only insofar as a weakened constitution inherited from pellagrous parentage might predispose to the disease."

*Tambroni* (1912) acknowledges, with limitations, heredity in pellagra: "Pellagra would transmit itself only when it is in activity (in atto) in the pregnant mother, that is, when there

exist manifest phenomena—nervous, cutaneous, gastro-enteric, etc. In the moments of truce, on the contrary, when the pellagra is found so to speak in the latent state, as is the case most of the time, the infant would be born immune."

*Franchetti* (1913) boldly asserts "as a conclusion of all the amount of work done one can affirm that a sure case of pellagra among nursing infants has never been observed, and that the few cases recognized all refer themselves to infants of age over one year, and in whom one was not able, with certainty, to exclude the influence of maidic feeding. In fact, none of the authors who have studied the disease, from the most ancient to the most recent, has ever had to infer that pellagra had a predilection for individuals of tender age." He goes on further to state—"it would have been very strange, that all the forms of infantile pellagra should have constantly escaped observation, unless one wished to admit in them a particular difficulty of diagnosis." Perhaps *Franchetti's* admission is responsible for failure of diagnosis in children, as he compliments *Sambon* in the latter part of his article regarding the ability of the former to be able to affirm the frequency of pellagra in infants. For instance, he cites statistics, 1911-1912. In 22 provinces there were only approximately fifteen cases of pellagra in infants, though the number of cases reported were in excess of 20,000.

*Peroncito* (1913) states "results equally interesting are had from an inquiry regarding the single cases. For example, this is most frequent, the

case of families in which, following altered economic conditions, there have manifested themselves suddenly new cases of pellagra, sometimes even several contemporaneously and specially in babies."

*Agnostini* (1913) interestingly states "while in opposition to that of healthy families the birthrate of pellagrous families is but little removed from theirs,—in these (pellagrous families) the figure of the mortality is truly impressive, as it exceeds the double of the common average.

"It is generally in the first three years of life that the offspring of pellagrins die marantic through chronic gastro-enteric catarrh, and often with eclamptic phenomena.

"The sucklings of pellagrous mother all have the same physiognomy which strikes one painfully by its suffering and oldish aspect, by the impressive thinness of the extremities. Born hypotrophic, with a weight and a length of body much below the average, they have an incomplete and very slow growth, so much so that at 3, at 4 years of age, they do not succeed in standing on their feet, they stammer a few syllables, the dentition has barely begun. A voluminous head of the pseudo-hydrocephalic type, badly shaped, with the fontanelles open up to 6 or 7 years of age, surmounts a rachitic little face, and raises itself badly on the neck, slender by reason of the hypotrophic and often atrophic thyroid. The thorax with the prominent sternum lets be discovered the costal arches distended below by the swollen and batrachian abdomen, with the umbilical cicatrix projecting. The

delicate extremities with the hypotrophic musculature are in marked contrast with the enlarged articulations. The skin of yellowish color, wrinkled and dry in the face, is often edematous in the face. The lips are violet and present easy ulcerations; the tongue is large and catarrhal; they ordinarily have diarrhea and gastric and intestinal dilatation.

"They are sad, querulous, insatiable, and rest little at night. This is the physiognomy common to these miserable ones, who—in the blood and in the maternal milk—find the deleterious principles which enfeeble the evolutive potentiality of their organisms.

"As for the milk of the pellagrous mother, I have verified it as insufficient in quantity, deficient in quality. From various analyses made, I have found that the apparent composition of the milk is not far removed from that of normal milk, except for an increase of salts and a diminution of casein; but without doubt there must pass into the milk those toxic principles circulating in the blood of the pellagrins, which determine the chronic catarrh of the digestive routes, the onset of convulsive phenomena. They contribute besides to the production of these phenomena, and to the defect of the nutrition, (contribute) to the scantiness of milk secreted, the prolonged nursing, the precocious and incongruous feeding of the sucklings.

"A clinical fact of the greatest interest has proved to me that the pellagrous intoxication of the father can influence in sinister manner the product of conception even if the mother is immune from pellagra. A healthy and robust peasant woman

(contadina) of the Reatino has for husband an individual affected by grave pellagra: of three offspring, two have died after a few months of life from eclampsia. The third, a daughter still living, is three years old, while she has the aspect of a six months infant, weighing only 5 kg., and being 60 cm long. The signs of the dystrophies of the tissues, and of the retarded development, are most accented.

"The head, which supports itself badly on the delicate neck, is asymmetrical and hydrocephalic, the face tumid, yellowish and oldish looking: one notes absolute lack of teeth, the thyroid body is atrophic, the abdomen swelled, the extremities delicate, the articulations enlarged. She has already been stricken twice with convulsive phenomena. Those among the born-pellagrous who survive the period of nursing are differentiated from normal children (a) by the disproportion between the age and the wretched development of the body, (b) by the late and uncertain walking, (c) the easy timidity, (d) the sad and suffering aspect, (e) the profound oligemia, (f) the yellowish skin often edematous and fissured on the back of the hands and of the feet, (g) the mucosa of the lips, violet and ordinarily ulcerated.

"Together with (a) the bad cranial conformation, (b) the asymmetrical face, (c) the slender and badly proportioned extremities, (d) the muscular atrophy—is notable the projecting of the epigastrium and the swelling of the abdomen by reason of the dilatation of the stomach and of the intestinal loops. They eat with voracity, they complain of a sense of weight

and of burning in the epigastrium, the salivation is troublesome and persistent, the chronic catarrh of the digestive routes is frequent and rebellious to remedies. One notes retardation of the speech center, ordinarily the psychic functions are slow, and scantily developed. They are melancholic, cry easily, and complain of continual sufferings.

"In the cases in which the pellagrous hereditariness from generation to generation cumulates and aggravates itself, these phenomena of physical and psychic degeneration reach the outside limits of idiocy, of nanism, of sexual dystrophy. The clinical types illustrated by me demonstrate this, in whom the arrest of development was so complete that at 18 to 20 years of age they presented a stature which did not exceed the metre, and the persistence of the fundamental physical and psychic characteristics of infancy. The importance of these cases stands also in the *fact*, that these forms of dystrophic infantilism, of myxedematous idiocy, in which together with the most marked arrest of the development, with the complete absence of the piliferous system, there is a sexual dystrophy so conspicuous as to present the penis and the testicles like those of a newborn, had not previously appeared in the families of the pellagrins of Umbria. In the cases in which the danger of infancy is survived, there continues in adolescence and in young the same retardation of the organic evolution; the muscular weakness persists, the oligemic state, the hypotrophy of the tissues, and there is a notable retardation of the epoch of puberty.

"From the statistical data collected by me, it results that the majority of the heredo-pellagrous children (fanciulle, girls) do not menstruate until they are 18 years of age, and the appearance of this is accompanied by vertigines, headache (cefalea), pains, is irregular and often substituted by troublesome leucorrhea. The slenderness of the extremities, the scantiness of the fat, the profound anemia, the lack of harmony of the lines of the face of the person, take from these unfortunates that attractive aspect which in the most beautiful period of life is the sole appannage of the daughters of the poor man. In the males we have ordinarily a stature inferior to the average, and extremities badly proportioned.

"In expectation that the law against pellagra may come, however opportunely modified, to prevent the diseased of pellagra increasing further, it is necessary meanwhile and quickly to provide for this, that the pellagrous women during the last period of gestation are re-invigorated with a suitable alimentary treatment, or removed at least in that time from the deleterious action of the toxic principles of spoiled maize. The nursing of the offspring ought to be as a rule forbidden to women affected by pellagra. But the gravest difficulty which in practice the actuation of this provision would encounter, counsels a modification of the postulate in the sense of assuring to the nurse at least during nursing a feeding healthy and sufficient. This can be done by means of the aids of nurse's pay (baliatico) in the places where it may not be possible to send these patients into the pellagrosaria.

The pellagrosaria in my opinion, ought to have special sections for refuge of the pregnant mothers and of the nurses.

"I have also noted in the families attacked by pellagra for the first time, ordinarily the adults and the old fall sick—in the families in which the disease is hereditary, there are observed cases of intoxication not only in the adolescents, but also in the infants of tender age.

*"Conclusions:*

"1—The maidic intoxication of the ancestors and specially of the mother in the period of gestation and of nursing, induces in the offspring a precocious exhaustion of the vitality, a more easy morbidity, retardations, deviations, and sometimes arrest of the development of the body up to the last degrees of somato-psychic degeneration, to idiocy, to nanism, to sterility.

"2—The heredo-pellagrins present a special disposition to contract pellagra and speedily pellagrous insanity. In addition, pellagra figures frequently as unique factor of constitutional neuropathies and psychopathies.

"3—Such slow and progressive hereditary degeneration, has already induced an evident and notable imperfection in the organisms of the rural populations in the zones in which the pellagrous endemic is more inveterate and diffuse: from this (the pellagrous endemic) (a) the elevated percentage of the mortality of those born heredo-pellagrins, (b) the continuous increase of the individuals—weak, dystrophic, sickly, incapable of military service; powerless to sustain the fatigues of the camps, fatally destined to populate



the refuges of beggary, the hospitals, the insane hospitals, with economic and social damage, progressive and incalculable."

In 100 heredo-pellagrous children under 20 years of age, he reported to have found 34 already attacked by pellagra, and with prevailing alterations of the nervous system and 15 of these were under 10 years of age. Of the 225 pellagrins up to the present time brought into the pellagrosarium of Citta di Castello, 73 are under 20 years of age, and of these (73), 21 are under 10 years of age.

*Raubitschek* (1915) writes: "But it is certain that in the better works of the last few years the belief is clearly expressed that even in pellagra regions not all individuals living under the same relationship succumb to the disease in equal manner. Aside from this, children, in general, seldom fall sick of pellagra; indeed infants remain exempt (perhaps in consequence of the nourishment with mother's milk and continuing same over a period of years); rarely seen in the first ten years, if the writings of *Fritz*, (1912), *Merk* (1909) and *Christoforetti* (1905) are correct."

*Niles* (1916) expresses the belief that heredity as a predisposing factor seems fairly well proved. He has records of 81 instances where pellagra was observed in the second or third generation and at present has under observation 28 cases where pellagra has occurred (most fatally) in the parents or grandparents. One instance, where an infant was born of a pellagrous mother, was reported. It seemed that conception took place during a re-

mission of the disease, but the confinement came on during the recrudescence. The infant lived only 2 months, never thrived and its skin was harsh and dry during the whole of its brief life.

*Muncey* (1916) in a very creditable study of the heredity of pellagra, concludes "that the data collected shows no evidence of direct heredity. There may, however, be an hereditary predisposition to the disease in those families in which chronic gastro-intestinal symptoms have existed for several generations. The relatively high proportion of gastric and intestinal diseases among pellagrous families would seem to substantiate this hypothesis."

*Rice* (1916) mentions as one of his conclusions, in a very systematic study, that "hereditary weakness was one of the predisposing factors operative in this series of cases."

*Davenport* (1917) believes "that pellagra is not an inheritable disease in the sense in which brown eye color is inherited. The course of disease does depend, however, on certain constitutional, inherited traits of the affected individual."

*Murphy* (1917) states that pellagra is neither hereditary nor transmissible from mother to nursing infant.

*Harris* (1919) in perhaps the most complete textbook written in the English language written on the subject of pellagra, mentions: "As to whether the malady is transmitted directly from parent to offspring we are still not in a position to determine, though the author is strongly of the opinion that this is the case. That deleterious in-



fluences are directly inherited where the parents suffer from the disease is clearly indicated by the fact that the offspring frequently exhibits physical malformations, curious asymmetries in the nervous system, and in a great number of instances early shows constitutional deficiencies, all of which can be explained but in one way. Assuming the truth of the author's thesis, that practically all of the pronounced clinical manifestations of this disease are the result of organic change, there can be no reason, a priori, why such alterations may not occur during embryonic life, and why pronounced symptoms of pellagra should not develop in infancy,—particularly where the child has not been properly nourished or has suffered from acute infectious processes. While it is true that we have no direct observations bearing on this point, the author feels under the circumstances that the view just expressed may be tentatively advanced, not only as an explanation of the typical pellagrous attacks in children, but of the other symptoms of ill health that the offspring of pellagrins so often exhibit, and to which attention will be more particularly directed in the succeeding pages."

*Voegtlin and Harris* (1920) preface their fourth article as follows: "Pellagra occurs only rarely in nursing infants, but undoubtedly the disease does sometimes appear during the first two years of childhood. The literature on pellagra contains a few brief references to this subject."

Later they described "the case of a breast fed pellagrous infant, five months of age, whose mother was evi-

dently free from the disease, the explanation of this particular case being on the basis of the vitamine hypothesis. In this instance, the mother living on a one-sided diet, may have retained enough vitamins for her own metabolism. Her milk, however, may have been deficient in this respect, with the result that her infant developed the disease."

*Goldberger, Joseph, Wheeler and Sydenstricker* (1920) state "the disease is rare at the age of 2 and under."

*Mitchnik* (1911) fails to state his opinion regarding hereditary pellagra but mentions, "among pregnant women, pellagra causes, as a rule, abortions; and when they have infants, they are sickly and degenerated."

*Fritz* (1896) calls to our attention "the pellagrosarium (Inzago in Province of Milano) has been open for 15 years, and the pellagrins received and treated are 1,285. Of these, with the exception of 40, all show the congenital pellagra constitution; the greater part from the paternal side, and with long scale ascending into the ancestors.

"Pellagra continues in those families which for years and years have been desolated by it, and those are the families in which the conditions alimentary, hygienic and of the artificial surroundings respond most to the causes of the fatal disease: in those families which are refractory to advice, to suggestions, and who wish to continue according to the measure of the past, even if it is deleterious and injurious."

*Mandolesi*, in a report made to one of the Congresses, said: "In some localities, where up to a few years ago pellagra was confined among those of advanced age, it has now rapidly involved also the youngest organisms."

Among some of the lesser authorities favoring hereditary pellagra may be mentioned *Maraglio* (1882), *Maragliano* (1879), *Gintrac*, *De la Fautrie* (1805), *Thiene*, *Babes* (1900), *Natalita*, *Roncoroni* (1890), *Devoto*

(1901), *Lavacher* (1905), *dell 'Isola* (1902), and *Lucantello*.

There is a smaller group who dispute the theory of inherited pellagra—*Facheris* (1804), *Winterlitz* (1862), *Solar* (1741), *Fournier*, and *de Giovanni* (1824). The contributions of the latter group, in particular, as well as those mentioned above, are not based on the number of cases or studies that would justify conclusions affirming or denying the hereditary nature of this disease.

## Editorials

### *THE RELATION OF IODINE DEFICIENCY TO GOITER*

If any theory was ever accepted as a positively demonstrated fact, that of iodine deficiency as a cause of goiter has surely been accepted as beyond any question by the majority of the medical profession of the world and particularly by that of America. The writings of Marine, Kimball, Plummer, and others, have so impressed this view upon the American Medical and lay minds that any dissenting view from that which regards a deficiency of iodine as the cause of simple colloid goiter must surely be regarded as a rank heresy. Nevertheless, the old infectious theory still has a few adherents; as does also the view that there are other factors concerned in the etiology of goiter besides a lack of iodine in the food or drinking water. In an article in the November Annals, Marine believes that in addition to an absolute iodine deficiency as a cause of goiter, there may also be factors bringing about a relative iodine deficiency by increasing the needs of the organism for thyroxin. Among the more important of these factors he mentions food, pregnancy, infectious diseases, and puberty. In winter cabbage there is found a stable goitrogenic substance; in summer cabbage an unstable anti-goitrogenic substance. Neither substance has yet been isolated. That

there would appear to be some other factor concerned in the etiology of goiter besides a simple lack of iodine is indicated by the fact that there are regions in the world especially rich in iodine content, and yet goiter occurs in such regions. The inhabitants of the Vistula delta live in such an iodine-rich country. They excrete large amounts of iodine; their blood-iodine is double that of the normal; their food contains 8-10 times the necessary amount of iodine; and the thyroids of these regions have a much higher iodine content than the normal amount of 3-6 mg.; and in spite of this superabundance of iodine, goiters occur. According to Liek, there has been since the War an increase in goiter in this region, although no apparent change in the food content of iodine has taken place. Further, in this region iodine has no specific action against goiter. Moreover, Oswald has shown in mountainous regions of endemic goiter that some thyroids, in spite of the iodine deficiency in food and drinking water, have the power of combining large amounts of iodine, so that some goiters possess a relatively high iodine content. Hellwig of Wichita, Kansas (Klin. Wochschr., October 11, 1930, p. 1913) has approached the problem experimentally, using rats as the classic animal for thyroid experiments. He found that rats fed for 160 days upon a diet deficient in

iodine showed atrophy of their thyroids instead of the compensatory hyperplasia described by other investigators. The poorer the food in iodine, and the longer such iodine-poor diet was given, the more marked the degree of thyroid atrophy. Hellwig regards this as proving the correctness of Wegelin's view that atrophy and not hyperplasia of the thyroid is to be expected, when iodine, the activator of the thyroid function, is deficient in the food. Without denying the prophylactic effects of a high iodine-content in the food in the genesis of goiter, Hellwig holds the view that endemic goiter is by no means proved to be of the nature of a compensation for the iodine deficiency; but he is convinced that the true cause of goiter is one, or several, positive factors. He finds this in the high calcium content of the drinking water of the goiter regions. More than fifty years ago this view was advanced by McClelland, Bouchardat, Billiet, and Boussingault. More recently Pighini and Abelin, who demonstrated an antagonistic action between calcium and thyroxin, have pronounced in favor of this theory. Wilms and Repin demonstrated that goiter-water lost its strumigenic effect in animal experiments when the calcium salts were precipitated by concentration in a vacuum. Geological investigations by McCarrison in Chivral, and Gilgit in Northern India showed that the richest goiter regions were associated with limestone formations. Also Tanabe produced the most marked goiters in rats on an iodine-poor diet, but which were given at the same time water rich in calcium. Hellwig studied the influence of water rich in

calcium on white rats maintained on an iodine-poor diet. In all of the rats so treated the thyroids showed significant enlargement and hyperplasia. Microscopically these goiters presented the appearance of a pure epithelial hyperplasia. Hellwig regards the positive factor to be the high calcium content of the water. When associated with iodine deficiency, the thyroid responds with the more intensive degree of hyperplasia—the parenchymatous goiter—when the food is rich in iodine, the excess of calcium leads to the production of a diffuse colloid struma. Hellwig apparently sees no essential difference between parenchymatous and colloid goiter; the two forms according to his opinion represent simply different degrees of reaction of the thyroid to the same goiter-producing agent with different iodine-content of the environment. In other words, colloid and parenchymatous goiter are both due to a single specific cause (calcium); the kind of goiter is due to the iodine-factor; parenchymatous when iodine is lacking, colloid when iodine is abundant. The weak point about this view is that Hellwig apparently has no conception of the constitutional factors underlying Graves' syndrome, and that the part played by the thyroid in Graves disease is a purely secondary one, and that the pathologic constitution remains even after thyroidectomy. Without the constitutional anlage there can be no Graves' disease. The great problem is what is the relationship between the thyroid and the Graves' constitution? The solution of this is not so easy as the article by Hellwig would indicate. Colloid goiter and parenchymatous goiter

cannot be different degrees of reaction to the same specific cause. The Graves' constitutional is congenital, familial, and hereditary. Upon this constitutional foundation an abnormal hyperthyroidism may or may not develop. When it does, Graves' disease is the clinical result. As Moschowitz has recently pointed out, the cause of this hyperthyroidism is usually psychical trauma. But the pathologic picture in the thyroid underlying the full-blown Graves' disease is that of a parenchymatous goiter. And this is always associated with the general pathologic features of the thymico-lymphatic constitution. This extremely important fact would seem to have escaped Hellwig's attention.

#### THE ROLE OF *STREPTOCOCCUS HEMOLYTICUS* IN SCARLET FEVER

The problem of the etiology of scarlet fever and the rôle played therein by *Streptococcus hemolyticus* still seem far from being settled, according to the Report of the Health Committee of the League of Nations, and much experimental work carried out during the last three years. Specificity of the Dick toxin has been questioned or denied by numerous investigators, among whom may be mentioned Bürgers, Cooke, van Gröer and Redich, Friedemann, Meyer, Molkte, Paris and Okell, Smith, Wheeler, Wadsworth, Zlatogoroff and Derkatsch. Ciuca and Satake were unable to produce experimental scarlet fever in a large series of Dick positive human volunteers by swabbing or injecting their tonsils with freshly isolated cultures of scarlet fever streptococci or scarlet fever

blood. The serological specificity of *Streptococcus scarlatinae* is not granted by Bürgers and Wohlfeil, Ciuca, Friedemann, MacLachlan and Mackie, Smith, Wordsworth, Williams, Zlatogoroff and Derkatsch, and numerous other investigators. The failure of the scarlet fever antitoxin to abate septic complications is generally admitted. Because of these discordant results and the apparent lack of agreement with the group maintaining the streptococcus etiology of scarlet fever, the filterable virus theory of this disease has again been brought to the fore. Zlatogoroff claims to have demonstrated that during the incipient stages of scarlet fever there is a filterable virus present in the faucial exudate which is capable of activating the otherwise ubiquitous and avirulent hemolytic streptococcus to take on toxigenic and pathogenic properties by which the clinical picture of scarlet fever is produced. When injected either intravenously or subcutaneously in rabbits, monkeys, and man, the filtered and sterile scarlatinal exudate almost constantly produces the scarlet fever syndrome, with typical histopathological lesions, as well as changes in the blood picture, analogous to the epidemic form of the disease. The experimental disease confers immunity for over two and a half years against reinfection. In rabbits and monkeys the virus alone is capable of producing the diseases in the absence of hemolytic streptococci, and yet, upon recovery, the blood-serum contains agglutinins for hemolytic streptococci. When suspended in Ringer's or Locke's solutions this filterable virus resists dispersed sunlight for 33 days at room temperature, and remains active for 35



days when left in the dark. In 0.5 percent phenol it remains viable for 15 days, and heating for 1 hour at 60°C completely destroys it. Birkhaugh, Ackerman, and Allen (Proc. Soc. f. Exper. Biol. and Med., Nov., 1930) attempted the production of the scarlatinal syndrome with whole and filtered scarlet fever faucial exudate from early and moderately severe cases of scarlet fever, according to the method of Zlatogoroff. From this experimental investigation, they concluded that sterile filtrates of scarlatinal faucial exudations failed to produce the scarlatinal syndrome in guinea pigs and rabbits. Subcutaneous inoculation of the unfiltered scarlatinal faucial exudations into guinea pigs and rabbits produced irregularly an erythema suggestive of scarlet fever, without any remarkable changes in temperature, leukocytic cell count or differential blood picture. Development of marked skin sensitivity to the Dick toxin following the injection of scarlatinal exudations suggested an allergenic basis for the suggestive scarlatinal rash which was followed by desquamation. Monkeys remained entirely refractory to the scarlatinal faucial exudations. A filterable virus in scarlatinal faucial exudations capable of producing the scarlatinal syndrome in guinea pigs and rabbits was not demonstrable. These investigations are, therefore, directly contradictory to those carried out by Zlatogoroff; it is difficult to explain such contradictions in the hands of apparently reliable investigators. Birkhaugh, Ackerman, and Allen's work contains no results that may be used against the Dick hemolytic streptococcus

theory. If anything, they rather tend to support it.

#### *THE CAUSE OF GINGER PARALYSIS DEFINITELY IDENTIFIED*

The cause of ginger paralysis has been determined. This paralysis, which has afflicted thousands of victims, is not caused by ginger at all, but by a compound known to chemists as tri-ortho cresyl phosphate. This chemical is the main constituent of technical tricresyl phosphate, which is widely used in trade circles, especially in the manufacture of varnishes, shellacs, and similar preparations. Being cheap and readily obtained in any quantities, it appears to have been used by irresponsible makers of so-called ginger extract to replace the ginger. There seems to be no question that the adulterated paralytic ginger extract contained tri-ortho cresyl phosphate in an approximate concentration of about two per cent.

The United States Public Health Service has been working on the public health aspects of "Jake paralysis" since the wide appearance of this condition in certain sections of the country last Winter and Spring. In attacking the problem, it soon became evident to investigators that they were dealing with a new form of paralysis and one in which many possibilities were involved. As the investigations proceeded, it became evident that some form of phenol was the causative agent. Soon attention was centered on technical tricresyl phosphate. Chemists of the Prohibition Bureau had found similar substances in suspected extracts. As a number of different



chemicals enter into the manufacture of this commercial product, it became necessary to separate them and find out what effect each might have if used in a beverage. This has been done and it has been found that tri-ortho cresyl phosphate either itself or in combination with other chemicals of harmless nature, when given to various kinds of animals will produce exactly the same kind of paralysis as that caused by drinking of "Jake". The Public Health Service has no record of a single case of paralysis caused by ginger preparations manufactured by reputable pharmaceutical concerns. Tri-ortho cresyl phosphate is, therefore, definitely established as the specific cause of the cases of so-called "ginger paralysis".

Studies conducted on laboratory animals show conclusively that a paralysis of the extremities can be produced uniformly in monkeys and other animals by the injection under the skin or by oral administration of the chemically pure as well as the technical tri-ortho cresyl phosphate. The failure to produce any symptoms, whatever, in monkeys with enormous

doses of this poison given by mouth indicates that it is practically not absorbed from the intestinal canal in that species.

The precise reason for including this remarkable substance as one of the ingredients of a substandard fluid extract of ginger made and sold for beverage purposes will probably never be known, unless a confession is wrung from the guilty ones. It seems entirely reasonable, however, to suppose that it was included on account of its physical or other properties which make it difficult to distinguish from the normal ginger constituents. Only a chemist of considerable ability could have thought of this; and had there been anything known about the pharmacologic action of this substance and the possible dire consequences, it is probable that it would never have happened. From this the question naturally arises as to whether there are not many other organic compounds of great medicinal interest, perhaps some with great possibilities for the treatment of disease, awaiting the attention of investigators.

## Abstracts

*Treatment of Peptic Ulcer with Gastric Mucin.* By SAMUEL J. FOGELSON (Introduced by A. C. Ivy), (Proc. of Soc. f. Exper. Biol. and Med., November 1930, p. 138).

The capacity of mucus to lower the free acid in the stomach is frequently suggested in the literature on gastric secretion. Lim determined that the concentration of the mucus in the stomach is highest at the lower secretion rates. The present problem was to determine the effect of increasing the mucus content of the stomach upon the free HCl. To evaluate the antacid effect of gastric mucin, it was necessary to either stimulate the secretion of mucin or to administer mucin by mouth. In these experiments attempts at stimulation failed to give consistent results, therefore a neutral preparation of hog mucin was prepared. Two ounces of this mucin in the stomach of Pavlov pouch dogs, after stimulation with 1 mgm. of histamine, was found sufficient to keep the stomach free of free HCl despite the fact that the pouches in these dogs showed adequate gastric secretion. Free HCl would always be present if the same experiment were performed and egg albumin, gelatin or meat substituted for the mucin. When half an ounce of mucin mixed with a pound of meat was fed the dogs, no free HCl was present during an observation period of 5-7 hours. These results suggested the treatment of peptic ulcer with mucin. Since January, 1930, twelve patients with definite ulcer histories and typical x-ray findings of peptic ulcer were made available for study. In addition to the customary bland diet, one ounce of powdered mucin was added to each meal and about 1 gm. of mucin in tablet form was given hourly. All of these patients were relieved of subjective symptoms within three days of treatment, and as yet there has been no

recurrence of the pain in observation periods extending over 2-5 months. This work is very suggestive of the addition of a useful substance in the symptomatic treatment of gastric ulcer. If the pain of ulcer, which is so important to the patient, and so often controlled with imperfect success, can be overcome by such a simple method of treatment as successfully and completely as indicated by these experiments, the use of mucin in the treatment of gastric ulcer will be of great value. This can easily be tested out by any one having a patient with gastric ulcer.

*The Therapeutic Use of Potassium in Certain Cardiac Arrhythmias.* By JOHN J. SAMPSON and EVELYN M. ANDERSON (Proc. of Soc. of Exper. Biol. and Med., November, 1930, page 163).

The investigation of the action of potassium salts on the heart dates from the time of Ringer's classical experiments on the frog heart. He proved, irrespective of osmotic tension, the necessity of sodium potassium and calcium ions in a balanced solution. Hering stopped paroxysmal ventricular tachycardia and ventricular fibrillation in the dog, and many investigators have similarly obtained immediate cessation of both auricular and ventricular ectopic rhythms by intravenous or intracardiac injections of solutions of potassium chloride. Wiggers suggested the possibility of its therapeutic use in ventricular fibrillation of accidental electrocution. It thus seemed reasonable to attempt to disturb the calcium potassium ratio in favor of potassium for certain other therapeutic reasons. Potassium salts were, therefore, used clinically to check attacks of paroxysmal ectopic ventricular tachycardia, and to prevent the occurrence of auricular and ventricular ectopic beats. Four different solu-

ble potassium salts were used: potassium chloride, potassium iodide, potassium citrate, and potassium acetate, all with apparently identical effect. It is presumed that the anion and acid-base influences are negligible. For later use, we have employed only the acetate, because it causes no gastric irritability when administered in raspberry syrup or similar menstruum. It was found that potassium may be safely administered orally in doses of 1-5 gm. of certain soluble salts, to human cases of heart irregularities. In 12 cases of such oral administration in auricular or ventricular ectopic beats or tachycardias, definite control of the arrhythmias was obtained in 5 cases. In Case No. 1, of this series, two attacks of paroxysmal centricular tachycardia, with duration 8 hours and 4 days respectively, were checked within the period of expected absorption time for potassium. Of the remaining 7 cases, 4 were free of any other evidences of cardiac pathology; and of these 4, none showed even a suggestion of any response to potassium. The failure to affect this group may be used to differentiate such patients from those with true myocardial damage. A low potassium content of myocardium is known to exist in cases of heart muscle failure, and may be the explanation for this difference in response. The influence of potassium on the arrhythmia occurred in 30-90 minutes after administration: and the necessary dose varied in different individuals. The effect was maintained from 6-8 hours, and occasionally some effect was observed for the succeeding 24-48 hours. A definite effect on the electrocardiograms in certain cases after potassium administration was observed. Certain ill effects are occasionally noted, namely gastric distress and diarrhea. The acetate and citrate caused less distress than the chloride or iodide. The paroxysmal nodal tachycardia observed in one case, and the epistaxis and petechiae in another may have been due to the potassium administration. The investigators conclude that potassium salt administration by mouth is effective in checking auricular and ventricular ectopic beats and tachycardia in the majority of cases of organic heart disease.

The failure to affect arrhythmias in patients without other evidence of cardiac pathology may be used to differentiate this group from the former. Potassium administration does not prevent the occurrence of auricular fibrillation.

*Pathological Lesions Produced in Rabbits Following Intravenous Injection of Concentrated Scarlet Fever Toxin.* By K. E. BIBKHAUG and R. P. HOWARD (Proc. Soc. of Exper. Biol. and Med., November, 1930, p. 95).

In a number of papers Duval and Hibbard have reported the production in rabbits of an acute glomerulonephritis following the intravenous injection of the bacteria-free toxic principle of *Streptococcus scarlatinae*, which they characterized as endotoxic in nature. Their histopathological material was considered analogous to that observed in human scarlatinal glomerulonephritis. These experiments were repeated by Reith, Warfield, and Enzer, who concluded that identical renal lesions occurred in normal rabbits as well as in those injected with suspensions of non-scarlatinal streptococci. They averred that none of the renal lesions produced were typical of human acute glomerulonephritis. On the other hand, Rich, Bumstead, and Frobisher were able to produce glomerular damage in rabbits by the intravenous injection of bacteria-free filtrates of fresh broth cultures of a virulent strain of *Streptococcus viridans* isolated from the blood in a case of subacute endocarditis with renal involvement. Their histological material was typical of acute hemorrhagic glomerulonephritis. The object of the present investigation was two-fold: first, to study the degree of toxicity of the concentrated scarlet fever toxin in chinchilla and mixed rabbit stock, and secondly, to scrutinize carefully the specific destructive action of the concentrated scarlet fever toxin on the rabbit kidneys. Doses of unconcentrated and concentrated scarlet fever toxin varying from 0.05 cc. to 10 cc. were injected intravenously into chinchilla and mixed breed of stock rabbits. Although the chinchilla rabbits showed a relatively greater

susceptibility to the lethal action of both the unconcentrated and concentrated filtrates, a minimum and specific lethal dose was scarcely discernible either in the chinchilla or in the mixed breed. The doses causing death varied irregularly between 0.6 cc. and 5 cc. of the concentrated toxin. The stock rabbits which lived 24 hours after the injection were killed at that time, and studied for macroscopic and microscopic lesions. No remarkable macroscopic lesions were found in any one animal. Although minor pathological differences were observed in individual animals, the histopathologic picture as a whole was uniform, and the differences showed no correlation with dosage, number of injections, or type of rabbit employed. The renal vessels showed a moderate hyperemia, especially of the capillaries and smaller veins. Congestion of the glomerular capillaries was fairly marked in some sections, while only moderately in others. No hemorrhage was observed. The dominant picture was excessive tubular swelling, especially pronounced in the convoluted tubules. The cytoplasm of the latter was markedly granular, and the nuclei were only faintly stained. No definite necrosis not attributable to postmortem changes were seen. The tubular swelling was so severe in several sections that the tubular ends were pushed into the space intervening between the glomerulus and Bowman's capsule. No tubular casts were observed. The glomeruli were in general hyperemic without showing the least trace of hemorrhage. A faint-staining amorphous substance, resembling albuminous exudate, often distended Bowman's capsule. No cellular reaction was found in the interstitial tissue, glomeruli or tubules. The investigators concluded that a minimum and specific lethal dose of the concentrated scarlet fever toxic filtrate was not discernible in rabbits, although the chinchilla breed displayed a relatively greater susceptibility to the lethal toxic effects of scarlet fever toxin. The renal changes observed in the rabbit following intravenous injections of unconcentrated and concentrated scarlet fever toxic filtrates were not those of acute hemorrhagic glomerulonephritis, but were

rather analogous to lesions observed in milder forms of tubular damage.

*The Blacktongue Preventive Value of Minot's Liver Extract.* By JOSEPH GOLDBERGER and W. H. SEBRELL (Public Health Reports, December 12, 1930).

This study had been organized prior to the death of Dr. Goldberger and had been partly carried out under his direction. It has been shown that dogs on the basic blacktongue-producing diet No. 268 develop signs of blacktongue in a period which only occasionally exceeds 53 days. When Minot's liver extract, in a daily dose equivalent to 100 gms. of fresh liver was given to 5 dogs on this diet, the occurrence of blacktongue was prevented for a period of at least 185 days. Three of the animals were continued on the basis diet after discontinuing the liver extract; these animals then developed blacktongue in 54, 228, and 52 days respectively, thus further strengthening the presumption that the delaying effect was due to the liver extract. The same quantity of Minot's liver extract, given daily to dogs that had developed signs of blacktongue on the basic diet, caused a recession of symptoms in 4 out of 5 dogs and prevented a recurrence except for slight signs, in two of the dogs for at least 140 days. The period of observation was too short to warrant the statement that blacktongue would not have developed at a later date, and the possibility of fleeting signs of recurrence in two of the dogs may indicate that the quantity given was barely able to maintain the animals. The conclusion is drawn, however, that Minot's liver extract, given to dogs on a basic blacktongue-producing diet, in a daily dose equivalent to 100 grams of fresh liver, has a very definite delaying effect on the occurrence of symptoms, and when fed to dogs in an attack of blacktongue has a very definite curative effect. The most reasonable explanation for this action seems to be that the liver extract carries the antipellagric vitamin with it. In view of the evidence herein presented, it would seem that Minot's liver extract is a fairly good source of the antipellagric vitamin, and given in

larger quantity would be of value as a temporary expedient in the treatment of pellagra.

*The Nature of Graves' Disease.* By ELI MOSCHCOWITZ (Arch. of Int. Med., October, 1930, pp. 610-629).

Moschcowitz accepts the constitutional nature of Graves' disease, as described by Warthin; but admitting, as all evidence seems to show, that a constitutional factor forms the background of Graves' disease, the latter is by no means settled by giving a label. The word constitution has a wide connotation, especially in respect to show how far the elements forming such a constitution are congenital, hereditary or acquired. Moschcowitz has no doubt that this constitution is a familial trait and admits that part of the constitution is congenital, as in Warthin's sense. He has, however, no doubt that the psychologic aspects in this constitution are affected profoundly by environmental factors, in most instances by the influence of parents on children. Even if one admits that the neuropathic constitution is the potential of Graves' syndrome, it still remains to be explained why only a small proportion of patients with such constitutions develop the disease while others do not. There must be another factor, and this Moschcowitz maintains is psychic. In four-fifths of the cases fear bears a direct relationship to the onset of the Graves' syndrome. In about one-fifth of the cases a history of fear or sudden emotional crisis cannot be obtained. On deeper questioning it would appear that fear usually accompanies the infection or illness following which the Graves' syndrome has developed. Fear is undoubtedly the basis of most of the factors that have been cited as the cause of the Graves' syndrome. The history of mental trauma is so common in Graves' syndrome that many observers regard it as

a traumatic and anxiety neurosis. There is every evidence that excess of thyroid function represents the predominant evidences of Graves' syndrome. All evidence shows, however, that the hyperthyroidism is secondary and not primary. The characteristic hyperplasia of the thyroid gland in Graves' syndrome is therefore sometimes lacking. The greater preponderance of Graves' syndrome in the female sex is the result of the greater sensitivity of the psyche in the female. The racial incidence of the syndrome conforms to what one would expect of ethnologic sensitivity. It is uncommon in races of coarse mental fiber, and is commoner in those of subtler mental reactions and where the strain of existence is keener. Graves' syndrome is apparently a social disease of the higher civilization. In the development of the influences in which the disorder is likely to develop, religion, the social and political status, the availability of the country for sustenance, etc., are probably important. The relation of the psyche to the development of Graves' syndrome is shown in the rarity of this disease in children, in whom the adjustable reasoning and emotive powers are not fully developed. The determinations of the basal metabolism should not be regarded so much as a diagnostic sign of the Graves' syndrome as a measure of the most prominent symptom, namely hyperthyroidism, and therefore of activity. If the relation of the constitution to Graves' syndrome is recognized it will help to explain the many failures after treatment, whether medical or surgical. This constitution persists after any form of treatment, so that cure is never wholly obtainable. The most profound effect of thyroidectomy is on the basal metabolism. Furthermore, the constitution being profoundly influenced by environment, the treatment of the patient should not cease after thyroidectomy.



## Reviews

*Handbook of Anatomy.* Being a Complete Compend of Anatomy, including the Anatomy of the Viscera, a Section of Surgical Anatomy, a Chapter on Dental Anatomy, Numerous Tables, and Adopting the Newer Nomenclature Designated the Basle Nomenclature, Commonly Called BNA. By JAMES K. YOUNG, M. D., F. A. C. S., Late Professor of Orthopedics, Graduate School of Medicine, University of Pennsylvania; Late Associate Professor of Orthopedic Surgery, University of Pennsylvania, etc. Revised by GEORGE W. MILLER, M. D., F. A. C. S., Associate in Anatomy, Jefferson Medical College; Surgeon to Montgomery Hospital, Norristown, Pennsylvania. Seventh Revised Edition. 460 pages, 154 engravings, some in color. F. A. Davis Company, Philadelphia, 1930. Price in cloth, \$4.50.

That a seventh edition of this handbook has been called for speaks for its usefulness to students of anatomy. The author's original purpose was to lighten the labors of the medical student, and the editor of this revised edition has endeavored to carry this out. The result is a very concise and complete anatomical compendium, which can be recommended as a very convenient aid to the study of anatomy. The Latinized form of the Basle Nomenclature is used consistently in the text, plates and index. Where both the new and old terms are used the new is emphasized by its primary position. Some changes have been made in text where the construction seemed obscure. This book serves well the purpose for which it is intended; and may be recommended for such.

*J. George Adami.* A Memoir by MARIE ADAMI. Together with contributions from others, his friends, and an introduction by SIR HUMPHRY ROLLESTON, 179 pages,

with portrait. Constable and Company, Ltd. London, 1930. Price in cloth, \$3.50.

This interesting memoir of the life of J. George Adami is the result of the compilation of the main facts concerning his career by his widow, aided by many of his old friends and colleagues. During his long service as Professor of Pathology at McGill University, Adami became widely known and beloved in the States. He was a potent factor in the development of pathology in this country. From 1894 to 1922 he was an active member of the Association of American Physicians, its President in 1912, and contributed numerous papers of value to its programs. His views on medical education had a direct influence on our system of medical instruction. He saw the educational problems from the standpoints of both scientific and practical clinical medicine. His ideal of the proper Medical Faculty was one that would turn out well-trained and capable practitioners, with a training in science and possessing the scientific spirit. He believed in a complete cooperation between the Medical School and the Hospital. He championed the extension of the medical course and the development of five and six year combined courses. As a pathologist Adami was a fore-runner of the present-day conception of Pathology as a biologic science. He broke away from the old-fashioned tissue-pathology, and conceived his science as resting upon the broadest biological foundations. He was far ahead of his times in his views upon bacterial variation and "subinfection." He very early interpreted inflammation as essentially defensive and protective in character. He realized fully the importance of heredity and constitution in disease. He was an ardent follower of Ehrlich, and ingeniously transferred his side-chain theory to the explanation of heredity. As we now realize,



his textbook "The Principles of Pathology" (1909), was an epoch-making work in marking the transition from the old anatomical and cellular pathology to the new biological conception of the present day. In it were foreshadowed many of the chief principles of the medical philosophy of the modern epoch. Adami had also a strong practical side. He was active in enforcing the bearings of pathology on the practice of medicine and public health in its broadest applications. In Canada he was an active leader in anti-tuberculosis work; and in all phases of preventive medicine he exhibited the deepest interest. To those of us who had the good fortune to know him, Adami will always be remembered for his delightful personality, his general culture, and his appreciative spirit. He was a man of wide interests, and possessed of a broad charity; and in his attitude toward life, exhibited the best qualities of a true gentleman of the world.

*Bacteriological Technique.* A Laboratory Guide for Medical, Dental, and Technical Students. By J. W. H. EYRE, M. D., M. S., F. R. S. Edin., Professor of Bacteriology in the University of London; Director of the Bacteriological Department of Guy's Hospital, London. Third Edition. 617 pages, 238 figures. William Wood and Company, New York, 1930. Price in cloth, \$7.50.

The first edition appeared in 1902, and was reprinted in 1906; the second in 1913, and reprinted in 1915. In this new edition the author has incorporated the new and valuable procedures elaborated during the Great War, with the newer methods and media that appear likely to stand the test of time, together with the old and tried methods coming down to us from the pioneers in bacteriologic research. Much space and attention have been devoted to the adjustment of nutrient media to pH standards, and the correlation of these methods with the older titration procedures. Much care has been expended upon the chapters devoted to the chapters on media as a whole, since this section of the work directly affects the efficiency of the bacteriologic laboratory.

The methods applicable to animal experimentation have also been expanded; and the section devoted to bacteriologic analysis has also been extensively revised and somewhat enlarged. This volume presents the subject of bacteriologic technique much more fully than its usual presentation in the ordinary textbooks of bacteriology, and may be recommended as supplementing these, to those engaged in practical bacteriologic work.

*Recent Advances in Chemotherapy.* By G. M. FINDLAY, O. B. E., M. D., D. Sc., Wellcome Bureau of Scientific Research, London. With a Foreword by G. M. WENYON, C. M. G., C. B. E., M. B., B. S., B. Sc., F. R. S., Director-in-chief of the Wellcome Bureau of Scientific Research, London. 532 pages, 4 plates and 11 text figures. P. Blakiston's Son & Co., Inc., Philadelphia, 1930. Price in cloth, \$3.50.

The literature of chemotherapy, which dates from the time of Ehrlich, has now become so extensive that it is difficult for the individual to grasp satisfactorily its significance. With the exception of Kolmer's "The Principles and Practice of Chemotherapy," dealing especially with syphilis, there is no work available in English that gives an adequate survey of the present position of the subject from the point of view of general medicine. Since little progress has been made in the chemotherapeutic treatment of bacterial diseases, and still less in virus infections, the greater part of this work is of necessity devoted to the consideration of the action of chemical agents on diseases due to protozoa, spirochetes, and helminths. It is a relatively simple procedure to determine in the case of these parasites, whether the infection is influenced in any way by chemotherapeutic methods, whereas the detection of bacteria and ultramicroscopic viruses requires more elaborate cultural or inoculative tests. Moreover, these organisms are more easily influenced by chemotherapeutic agents than are bacteria and allied organisms. This book attempts to show the recent advances in chemotherapy. When the last ten years are surveyed as a whole, it is apparent that cer-

tain definite advances have been made in chemotherapeutic treatment, and that a better understanding has been gained of the mode of action of well-established medications. During this period the focus of attention has been shifted from a study of the direct interaction of drugs with infecting organisms to an investigation of the part played by the tissues in chemotherapeutic treatment. This book presents a very good and thorough survey of the literature. The material has been well analyzed and digested, and is presented in a clear and unprejudiced manner. It may be recommended as a thoroughly satisfactory exposition of the subject of chemotherapy up to date.

*Problems and Methods of Research in Protozoology.* Edited by ROBERT HEGNER, Professor of Protozoology, and JUSTIN ANDREWS, Associate in Protozoology in the Johns Hopkins University School of Hygiene and Public Health. 532 pages, 30 figures. The MacMillan Company, New York, 1930. Price in cloth, \$5.00.

This book is the work of twenty-five contributors and two editors. Specialists in the various fields represented have contributed chapters on problems and methods of research in the various phases of the subject about which they were most familiar. The editors have organized the volume with the purpose of aiding both the seasoned investigator and the beginning student. They have attempted to bring together information that is at present widely scattered in the literature or has not yet been published. The field of protozoology has become so highly specialized that each student at present gains a comprehensive knowledge of only one or two groups of protozoa, or of only one or several phases of their host-parasite relations. Consequently it has become difficult for an investigator in one field to keep abreast of the problems and methods of research in other fields. The student who wishes to specialize in protozoology is unable to secure in any easily accessible form an adequate idea of the field of such study, its problems available for investigation, and of the methods that may be employed in their study. The material

and its treatment make of this book a highly specialized volume not adapted to the use of the ordinary medical student or practitioner. It serves well the purpose for which it was designed, that of giving aid to the special student and investigator in the field of protozoology. Its interest is scientific rather than clinical. Nevertheless there is much scattered through its pages that bears practically upon medicine.

*Diet in Disease.* By GEORGE A. HARROP, JR., M.D., Associate Professor of Medicine, Johns Hopkins University; Associate Physician, Johns Hopkins Hospital. 404 pages, 80 tables, Sample Diets and Food Lists. P. Blakiston's Son & Co., Inc., Philadelphia, 1930. Price in cloth, \$3.50.

This book embraces the material used by the writer in lectures, ward rounds, and clinics to the third and fourth year classes at the Johns Hopkins Medical School on the use of diet in disease. It includes a brief survey of the general principles of nutrition which have particular bearing on clinical dietetics, together with a brief account of the principal foodstuffs and their place in the diet. Long tables of food values have been omitted, as they are obtainable elsewhere, only those have been included of which a working knowledge is of particular value. Some information as to the best methods of preparing certain important foods is also considered useful. Most of the diet lists given have been used in the wards or in the out-patient department of this hospital, and have been tested by trial and experience. Most of the weights of average servings of the foods as given in the food-tables have been redetermined, and in some instances will be found to differ rather widely from figures given in current text-books. The author emphasizes the important fact that some working knowledge of dietetics is necessary to treat disease and to outline dietaries for the sick. The medical student should have some understanding of the principles of nutrition; but unfortunately he is too often left to his own resources in this matter. He usually falls back upon the complicated diet lists which are found in many textbooks; only to be-

come discouraged at the hopelessness of committing to memory all of the numerous and often unrelated material. The author also warns against the dangers of following a traditional routine for a given disease regardless of the all important particular needs of the individual patient. Such a procedure may cause positive harm to the patient. Deficiency disorders as a result of improper dietary treatment are not uncommon. Patients with duodenal ulcer may develop scurvy, or patients with nephritis may suffer from protein deficiency. It would be far more useful to give the student a comprehensive knowledge of principles and some idea of the value and use of the foodstuffs which compose the diet. If he masters these elements he is free to formulate his own treatment in the same way that he administers any other therapeutic agent. Not every patient with albuminuria requires a low protein diet any more than everyone with heart disease requires digitalis. The book seems eminently sane, and is clearly and concisely written. He treats of such matters as high protein diet on the basis of facts alone, and not from any preconceived opinion or prejudice. The perusal of this book is recommended to senior medical students, internes, and house physicians.

*Tonsil Surgery.* Based on a Study of the Anatomy. By ROBERT H. FOWLER, M.D., Chief Surgeon of the Tonsil Hospital, New York; Junior Surgeon (Throat Service), Manhattan Eye, Ear, Nose and Throat Hospital, New York. 288 pages, 103 illustrations, including 10 full-page color plates. F. A. Davis Company, Philadelphia, 1930. Price in cloth, \$10.00.

This book is written pre-eminently from a surgical standpoint. It is intended primarily for those who seek information on the best types of operation, and knowledge regarding the physical aspects of the tonsil and its attachments as they bear on the operative technic. In it the author presents a hitherto unemphasized phase of tonsil surgery upon which information has been prepared and authenticated so recently that the facts have not been presented in so complete a form before. Through the discovery

made by the author in collaboration with Wingate Todd, of the tonsillopharyngeus muscle and of its relations with the capsule, a marked improvement in the technic of tonsillectomy has been achieved. The new operation removes the whole tonsil in its capsule without trauma to other tissues, and leaves the fossa covered with an intact fascia. On such a surface infection does not spread easily, and the operation is made as safe as possible. This is undoubtedly a great advance in the technic of tonsillectomy. The book is concerned chiefly with the how of tonsillectomy, and not with the why of it. The medical man will find the book deficient in matters of symptomatology, etiology, and pathology.

*Stalkers of Pestilence.* The Story of Man's Ideas of Infection. By WADE W. OLIVER, M.D., Professor of Bacteriology, Long Island College Hospital. Introduction by THEOBALD SMITH, M.D., Ph.D., Director, Department of Animal Pathology, The Rockefeller Institute. 251 pages, 23 illustrations. Paul B. Hoeber, Inc., New York, 1930. Price in cloth, \$3.00.

This is a reprint, with additions and corrections, from the American Journal of Surgery, Vol. VII, 1929. The volume traces briefly the historical development of man's ideas of the nature of infection and of infectious diseases. Five chapters: Prehistoric Man to Hippocrates; Arabic Medicine, The Medieval Period and the Renaissance; The Seventeenth and Eighteenth Centuries; the Nineteenth Century; and the Twentieth Century are devoted to this evolution of knowledge of parasites and parasitism. The transition from the primitive superstitions and mythologies of the earliest periods, through phases of belief in telluric, cosmic, and miasmatic influences, to a final understanding of the living agents of disease is a long and interesting tale; and it is very well told by Oliver. The author does not confine himself to his main thesis; his book is a condensed history of medicine as a whole, until he reaches the nineteenth and twentieth centuries, where naturally he devotes himself more particularly to his theme. Since infection plays so important a part

in modern medicine, the history of medicine for the last fifty years is concerned chiefly with the development of bacteriology and parasitology, and the secondary branches of serology and immunology. The illustrations are well chosen from the great ones of medicine who have marked epochs of medical thought. The book is a well-written one; it possesses an interesting style; and the facts are told in a clear and concise manner, without vagueness or over-detail. The main facts of this great development of human thought are here; and their evolutionary relationship clearly traced. This is a

good book for the medical student to read while doing his courses in bacteriology. Teachers of bacteriology would do well to include it in the list of reference works to be read by the student; or even to require it as part of the regular work. It is becoming more and more the custom, and a very happy one it is, of tracing the historical development of each subject, anatomy, physiology, pathology, etc., in connection with the regular work in the given line. We suggest that active teachers of bacteriology could make good use of the present volume in the same way.

## BALTIMORE—WHERE WE MEET

(American College of Physicians, March 23-27, 1931)

A CITY of active industry and commerce which preserves despite its progress something of an atmosphere of deliberateness—almost conservatism, a city of busy factories, piers, railroad stations, offices, office buildings, shops and markets from which almost every worker goes home to his own hearth,—this, in brief, is Baltimore. Seen from the air, it is for the most part a cluster of flat-roofed dwellings hugging the two branches of the Patapsco River, which here is nothing more nor less than an estuary of the Chesapeake Bay. Around the winding shore line are miles and miles of wharves, factories and railroad yards. A little farther back from the shore, in a compact group, are the towering centres of the city's finance. Then, surrounding these, lies a sea of homes studded here and there with green islands of park or public square, or with the domes and spires of churches, museums and institutions of learning. And around all these, in



FIG. 1. Air View of Baltimore.



turn, lie exceptionally lovely suburbs and a rolling countryside which finally merges in the foothills of the Appalachians. Scarcely an American city, unless it be one of the Western Coast, enjoys a more attractive environment. Scarcely a city in the world, unless it be London, disguises its activity so completely, or more deeply impresses one with the sense that the business of the individual is the living of a life rather than the making of a living.

Founded in 1729, Baltimore was named after the domain of the Calverts, the Lords of Baltimore in Ireland. Having lived and grown through the Revolution, the War of 1812, the Civil War, and the World War, the city has, consequently, acquired a rich store of historical connections, many

of which have left tangible memorials behind them. Attached to the streets of the city one may notice the names of Revolutionary heroes—Washington, Lafayette, Pulaski, Greene and Howard. The first monument in the United States to George Washington was erected in Baltimore in 1815. Many years later, in 1924, a bronze equestrian statue to Lafayette, his companion in arms, was placed near the base of this monument, a fitting addition to a section named Mt. Vernon Square, after Washington's homestead.

In the War of 1812, Baltimore gave birth to the National anthem, The Star Spangled Banner. Baltimore "privateers" had played such havoc with the British shipping that Admiral Cockburn determined to exterminate this



FIG. 2. Mount Vernon Place—Baltimore— showing Washington Monument, the first monument erected to the Father of our Country.



"nest of pirates." On September 13, 1814, however, he met a severe defeat off Fort McHenry and was convinced of the folly of this determination. Watching the battle through the night, Francis Scott Key was inspired to write the lines which are now familiar to every American citizen. Fort McHenry dates from 1775. As a unit of defense, it is now obsolete; but Federal and private resources are being expended to preserve and cherish it for its obvious historical value. It lies only a few minutes from the centre of the city on a point of land marking the division between the two branches of the Patapsco.

In the Civil War, Baltimore was regarded as one of the Border-Line cities. Yet, on April 19, 1861, the first blood of this war was shed when a Massachusetts regiment passed through Baltimore on its way to Washington. This was at Camden Station, on the Baltimore and Ohio Railroad, a station which still stands, essentially unaltered in external appearance, in the southern part of the city. Perhaps, in the last analysis, the sentiment of the city was actually more Confederate

than Border-Line; and the Confederate Soldiers' Home, at Pikesville, now occupied by a fast dwindling number of inhabitants, is a point of interest. Within easy reach of Baltimore are the battlefields of Antietam and Gettysburg; while the Shenandoah Valley, replete with Civil War history, is a place of pilgrimage for hundreds of Baltimoreans annually in apple-blossom time.

Redwood Street, formerly German Street, one block south of Baltimore's central thoroughfare, bears the name of the first American soldier killed in the World War—a Baltimorean. The War Memorial, just across from the City Hall, is of interest for the beauty of its own construction as well as for the records of Baltimoreans and Marylanders in the struggle only recently ended.

But this is only a portion of Baltimore's historical aspects. Industrially and commercially, the city has seen many interesting developments. From its very foundation, Baltimore gave promise as a port of great advantages. Behind it, notably in Frederick County, lies one of the richest agricultural sec-



FIG. 3. Fort McHenry—Baltimore, the birthplace of the Star Spangled Banner, our national anthem.



FIG. 4. Civic Center—looking west from War Memorial across Memorial Plaza to City Hall in background.

tions of the country. Through the city, outward-bound, have passed throughout the years, the products of this rich hinterland; while inward-bound have passed the countless tons of imports necessary to the development of the South and West. Here were built the swift, strong Clipper ships which, in numbers almost legion, outsailed all

other craft of their day and brought to port thousands of tons of coffee, sugar, molasses and choice West Indian tobacco—not to mention innumerable hogsheads of Jamaica rum.

The list of "firsts" for Baltimore is a lengthy one. To enumerate all its items would appear egotistical. Nevertheless, some of them can be given

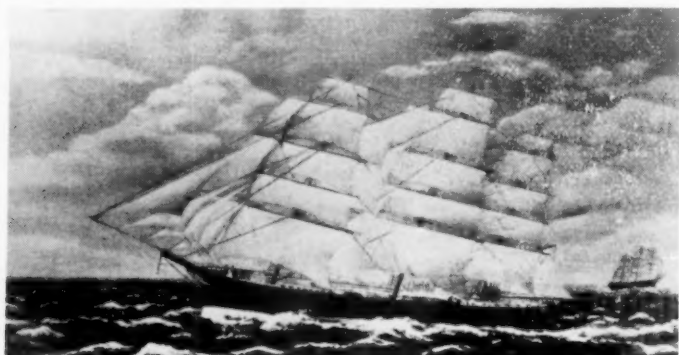


FIG. 5. The "Mary Whitridge"—typical of the Baltimore Clipper Ships.

with quite pardonable pride. Here, in 1828, was established the Baltimore and Ohio Railroad, the first railroad in the country to initiate and continue a commercial service. Mt. Clare, the first railroad station in America, still stands on West Pratt Street, within walking distance of the University of Maryland School of Medicine. It now serves as the construction and repair shops of the Baltimore and Ohio. From it ran the "Old Main Line," the road's first stretch of track, which followed the shore of the Patapsco to Ellicott City, and subsequently to Frederick and the West. From this station, in 1844, was sent to Washington, D. C., the first Morse telegraphic communication in the United States.



FIG. 6. Mount Clare—first railroad depot in America.

Baltimore was the city in which Mergenthaler brought the linotype to a working status. From his first commercially practical machine, made in 1890, have sprung the vast developments in modern printing which now make possible such publications as this.

Gas, for illuminating purposes, was first made here in 1816; and we are

told on the authority of Cordell that Baltimore was the second city in the world—London being the first—to use this gas for the lighting of public highways. Charles Varle, an engineer who writes of Baltimore in 1833, naively comments on the efforts of the Baltimore Gas Works to boost the sale of the resultant coke. As for the coal tar, likewise resultant, he informs us that it offered an excellent preservative for ship timbers. This was before the days of the modern steel industry and those wonderful chemical advances which now give us over 5,000 dyes from coal tar, a host of artificial perfumes and numerous drugs and medicines. Within view of the City Hall stands a greatly treasured memento of Baltimore's industrial history. This is the Shot Tower, said to be the only remaining structure of its kind in the world, a relic of the days before the du Ponts and the Krupps, when gravity was relied upon to mould the leaden balls.

Baltimore to-day is a city of 805,753 inhabitants. It contains about half the population of the State of Maryland. Of these inhabitants, some 62% are shown by Federal Census Statistics to live in houses owned by themselves or their families; and the long rows of two-story dwellings, each with its white marble steps, have often elicited comments from visitors. In population, Baltimore is eight among the cities of the country. The growth of the city has been steady and substantial. It has never enjoyed a boom or a mushroom growth. Nevertheless, to-day it ranks industrially as the seventh city in the country, its annual output exceeding \$700,000,000. As a

port, it is third in the Nation's foreign trade tonnage. It is second only to New York as an Atlantic Coast port, and ranks *first* in intercoastal trade westward via the Panama Canal. Its wholesale trade is annually \$470,000,000; and its retail, \$360,000,000. In the last two years, it has given promise of becoming the aircraft manufacturing centre of the Eastern portion of the United States. The city lies on three passenger air routes and has a municipally-owned air-port which, when completed, will cover 1,000 acres.

Because of its geographical location, Baltimore is closer to the productive centres of the West—likewise closer

to the centre of population of the United States—than any other Atlantic port. Consequently, it enjoys a lower freight rate differential than New York, Philadelphia and Boston. Through Baltimore are routed exports from 38 States and Canada, and imports from 33 States and Canada. Three railroad trunk lines, the Baltimore and Ohio, the Pennsylvania and the Western Maryland, connect the piers of the city with all parts of the interior.

Baltimore's industries to-day are highly diversified. Some of its manufacturing plants are the largest of their kind in the country—even in the world.



FIG. 7. Shot Tower—Baltimore—the last remaining tower used for the manufacture of shot. Cornerstone laid in 1828, by Charles Carroll of Carrollton.



FIG. 8. Row 2-story houses. One family residences typical of Baltimore.

These include the Baltimore Copper Smelting and Rolling Company, the Davison Chemical Company and McCormick and Company, The Sparrows Point Branch of the Bethlehem Steel Company, and the American Sugar Refining Company are largest plants of their kind located on tidewater. A large part of the industrial alcohol used on the Atlantic Seaboard is made here;

and here are carried on most of the oil cracking processes that result in the gasoline used in this same section.

By virtue of its proximity to the Chesapeake Bay, an inland sea with fifty tributary rivers, Baltimore plays a prominent part in the fishing industry. Annually 2,500,000 bushels of oysters are taken from this bay; and in the distribution of this one form of



FIG. 9. Roland Park Homes—part of the Roland Park, Guilford-Homeland Development, one of the country's most beautiful suburbs.

sea-food, both in its raw and canned states, Baltimore leads the country. Something to the same effect may be said of the blue crab, which, in normal seasons, is so plentiful that it can be scooped in nets from the bay's surface. The city's thriving canning industry is fed also by the surrounding agricultural region; for most of the tinned tomatoes used in the United States are put up here. In fact, both sea and land produce such a variety and abundance of good things to eat—among them the famous Maryland terrapin—that Oliver Wendell Holmes once called Baltimore the gastronomic centre of the universe.

In pursuing commercial success, Baltimore has not neglected intellectual development. To-day it is indisputably one of the medical centres of the world. It presents unusual facilities for the care of the sick, for research into the cause and cure of disease, and for the instruction of medical students. Almost indissolubly linked with

the name of Baltimore are the names of William H. Welch, Sir William Osler, Louis McLane Tiffany and John J. Abel, who in themselves have been termed epitomes of modern medicine. The city has two outstanding medical schools and more than 20 hospitals.

The fifth medical school to be established in the United States was founded here in 1807, under the name of the College of Medicine of Maryland. This institution, now the University of Maryland School of Medicine, has enjoyed an unbroken history of usefulness since its inception, supplying continuously most of the physicians of the State. Its central building, at Lombard and Greene Streets, which follows in general the external lines of the Pantheon at Rome, is the oldest building in the United States devoted to medical teaching. Here, for the first time in medical education, dissection was made a compulsory part of the curriculum; here, for the first time



FIG. 10. View of Baltimore Harbor.



in America, senior students were required to spend a portion of the year in residence in the hospital.

The School of Dentistry and the School of Pharmacy, both branches of the University of Maryland, date respectively from 1840 and 1841. The former was the first institution in the world to be devoted exclusively to dental surgery.

In 1876, the Johns Hopkins University and the Johns Hopkins Hospital were founded through the generosity of a Baltimore merchant, whose

name these institutions now memorialize. Blazing a new trail, and introducing into the United States what now is termed "graduate learning," the University, through the men it assembled at its start—among them Gilman, Remsen, Sylvester, Martin, Rowland—has given a tremendous impetus to American letters, science and education. At Homewood, on the upper stretches of North Charles Street, are the University's collegiate and graduate departments of the arts and sciences. Some three miles distant, in



FIG. 11. Part of Chesapeake Bay oyster fleet.



FIG. 12. University of Maryland.

close proximity to the Hospital, are the School of Medicine (opened 1893) and the School of Public Health and Hygiene (opened 1918).

Instruction in music is provided by the Peabody Conservatory; that in the

plastic and graphic arts, by the Maryland Institute of Art. Just across the street from the Conservatory is the Walters Art Gallery, containing one of the finest private collections in the country. Both the Gallery and the

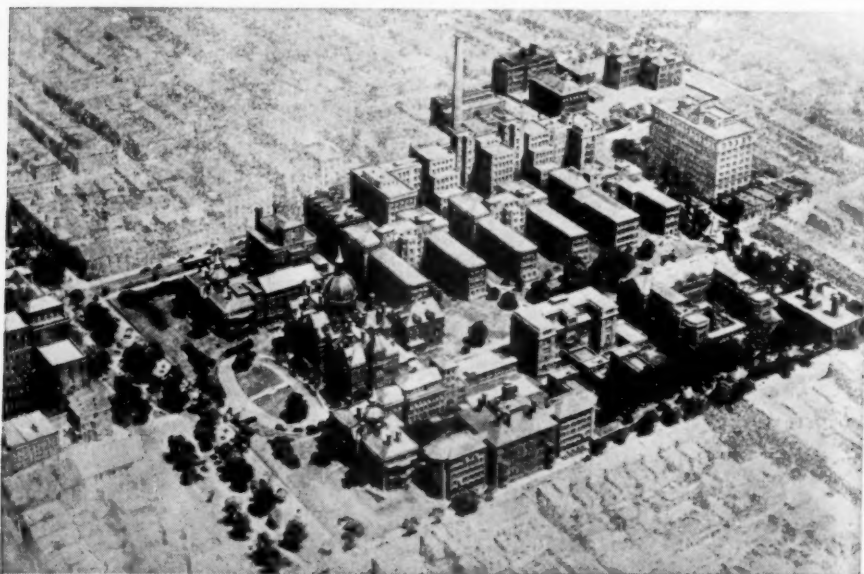


FIG. 13. Johns Hopkins Hospital Group.

Conservatory form a part of Baltimore's famous Mt. Vernon Square, which, in addition to its own lines and its imposing buildings, is interesting for the local and National history memorialized in the monuments that adorn it. In this square, moreover, may be seen some of Barye's best bronzes.

In addition to the institutions mentioned above, Baltimore contains Goucher College for Women, Loyola College, Notre Dame Academy, St. Mary's Seminary, and Morgan College (colored). Its library facilities are excellent. The Enoch Pratt Free Library (established 1882) has approximately 600,000 books available for circulation in the city. For the student and scholar, these are augmented by the reference library of the Peabody Conservatory (253,000 books), the library of the Medical and Chirurgical Faculty (38,000 books), in addition to the libraries of the University of Maryland and the Johns Hopkins University. The William H. Welch Medical Library constructed on an appro-

priation of \$750,000, from the General Education Board, was opened in 1929. This building is equipped especially for the collection, housing and utilization of medical works, as well as for the development of an Institute of the History of Medicine. Washington is so near, and the inter-library loan system so well managed that Baltimore scholars enjoy practically all the many advantages of the Library of Congress.

In literature, Baltimore has enjoyed an ample share. Much of the life of Edgar Allen Poe is connected with the city. Here he wrote "The Raven." The poet is buried in old Westminster Church yard, at Fayette and Greene Streets; and a statue has been erected to his memory at Wyman Park, near the Johns Hopkins University. Sidney Lanier, poet, musician and literary critic, was connected with Hopkins in its early days. Here to-day lives Lizette Woodworth Reese, author of the sonnet "Tears," and numerous other poems that have won her well merited renown.



FIG. 14. Peabody Institute established in 1868 by George Peabody.



FIG. 15. Grave of Edgar Allan Poe Westminster Churchyard—Baltimore.

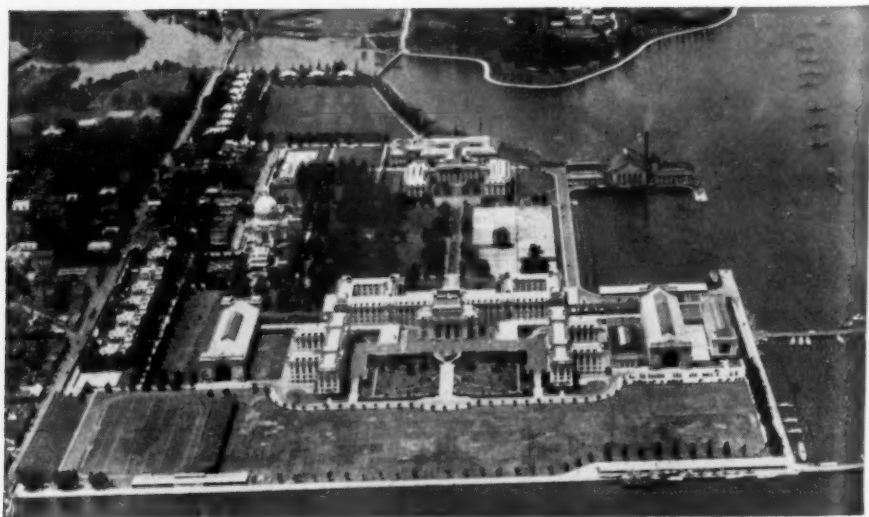


FIG. 16. Air View of the United States Naval Academy—Annapolis.

To continue about Baltimore would fill many pages; for a city which for over two hundred years has grown steadily in physical assets, giving heed all the while to the things of the soul—as Baltimore has done—will have much to say for itself. The truth of this will be seen most forcefully when one stops to consider how peculiarly vital in the experiences of the world have been the years from 1729 to 1931. But Baltimore is not all of Maryland. Distant only a pleasant morning's or afternoon's drive along good roads and through inspiring country, are Annapolis and Frederick. A well informed writer has said that were George Washington to come back to life, he would still feel perfectly at home in Annapolis, so lightly has the hand of

change rested upon it. Its outstanding points of interest are the beautiful old State House, St. Johns College and the United States Naval Academy. At the Academy rest the remains of John Paul Jones, the country's first admiral. In Revolutionary history, Annapolis is famous as the place of the burning of the "Peggy Stewart" in defiance of the tea tax. At Frederick, another wealth of historical associations lies in store, centering about the gallant stand of Barbara Fritchie.

Moreover, a wide boulevard, accommodating four automobiles at once, conducts one by an easy hour's drive to Washington, the Nation's Capital. Few, indeed, of those visitors from afar to Baltimore can resist this drive.

## College News Notes

### THE FORTHCOMING CLINICAL SESSION IN BALTIMORE.

The Fifteenth Annual Clinical Session of the American College of Physicians will convene in the City of Baltimore during the week of March 23, 1931. The privilege of meeting in this city was made possible through the cordial invitation of the Johns Hopkins University School of Medicine, the University of Maryland School of Medicine, the Medical and Chirurgical Faculty of the State of Maryland, the Baltimore City Medical Society, and the further coöperative interest manifested by the various Baltimore hospitals and civic societies. It is to be hoped that this meeting will at least equal in excellence those which have been produced in recent years in other cities; and it is the belief that all who will attend this meeting will find ample in the way of clinical, laboratory, research and historical interest, well to repay them for the time spent in making the journey.

Local conditions, as well as medical and hospital facilities, greatly affect and alter the construction of programs; and at this writing the actual titles of papers and clinics to be presented, by whom, when and where, are far from being in a completed and final state. Moreover, it is possible that for reasons, both of economy and others, the former precedent of issuing a preliminary program may not be lived up to, though this also is not final. In any event, the final draft of the program of the Baltimore Session will be in the hands of each member in ample time for him to peruse it carefully and make his selections well in advance of the actual time of the meeting. Nevertheless, it has seemed wise to issue a preliminary statement about the meeting in the form of a printed article, outlining thus nearly four months in advance the general scope and construction of the Clinical Week.

At the risk of repetition, the following points with reference to the meeting will bear repetition:

(1) *Time and Place:* March 23-27, 1931, in Baltimore, Maryland.

(2) *Hotel Headquarters* will be at the Lord Baltimore Hotel; and it is important at this point to emphasize the wisdom of making early hotel reservations, whether they be at Hotel Headquarters or at some other of the hotels listed at the end of this article.

(3) *General Headquarters*, at which the registration of members, commercial exhibits and all General Sessions will be held, will be the Alcazar, situated at the corner of Cathedral and Madison Streets. Baltimore, unfortunately, is not yet the proud possessor of a convention hall or auditorium at all adequate to its needs, nor comparable to the buildings of this sort found in cities of smaller population. Nonetheless, it is felt that the Alcazar will meet all of the requirements of the College meetings; and all of the meetings, exhibits, registration offices, etc., are located on the same floor, and in easy access to one another.

The skeleton outline of the entire Clinical Week is given in the diagram below, and certain points require particular emphasis:

(1) Those who are planning to attend the Clinical Session should arrange to reach Baltimore either Sunday evening, March 22, or Monday morning, March 23, since the morning of March 23 is left entirely open, thereby giving members and guests ample opportunity to get settled in their hotel quarters, register at the official registration office, and secure therefrom their cards for the various clinics and lectures, for which they have previously signed up, as has been the custom in the past. Not only are these details important, but it is equally to be stressed that a full attendance at the first



FIFTEENTH ANNUAL CLINICAL SESSION  
BALTIMORE, MARYLAND, 1931

Time	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
A. M.	March 23	March 24	March 25	March 26	March 27	March 28
9:00 to 12:30	Morning free. Registra- tion. Exhibits, etc.	3rd General Session	5th General Session	6th General Session General Business Meeting	7th General Session	Entire Day in Washington, D. C. Clinics, Inspection Tours, etc. Under Auspices of Medical Departments of Army, Navy, U. S. Public Health Service, and Georgetown University  Full details not yet ready.
12:30 to 2:00 P. M.	Lunch	.....	.....	.....	.....	
2:00 to 5:00 P. M.	1st General Session	1st Clinical Session	2nd Clinical Session	3rd Clinical Session	4th Clinical Session	
5:00 to 8:00	Dinner	.....	.....		.....	
8:15 to 10:30	2nd General Session	4th General Session	Convoca- tion and Reception to New Members	Annual Banquet	FREE	

General Session, to be held Monday afternoon, is not only desirable but is a courteous acknowledgment to the hosts of the entire meeting. It is the sincere hope of the Program Committee that the hall will be filled when the meeting is called to order sharply at 2 o'clock on the date above mentioned.

(2) It is to be noted that the Convocation this year will be held earlier than has been the custom in the past. Further reference to this will be made in a subsequent paragraph.

(3) It is to be noted that the Clinical Sessions of the meeting will occur in the afternoon, rather than in the morning. This plan has been adopted particularly for the reason that it interferes much less with the teaching of medical students at the Johns Hopkins Medical School and University of Maryland. It will be remembered that this same plan was followed at the meeting in New Orleans, with apparently just as great

success as when the sessions were reversed.

(4) The Annual Banquet will be held on Thursday evening, March 26, presumably at the Lord Baltimore Hotel; and to this, as in times past, ladies are cordially invited.

(5) After the Clinical Sessions have been finished on Friday, March 27, there will be held a Post-Clinical Session Day in Washington, D. C., for all those who care to attend what promises to be an extremely interesting and valuable meeting there.

#### GENERAL SESSIONS

At the last meeting of the Board of Regents that was held during the Minneapolis Session, it was decided that the President of the College would be held responsible for the programs of the General Sessions, of which there are seven in all. Following the Minneapolis meeting, the Executive Secretary of the College, Mr. Loveland, sent out a questionnaire to all of the Fellows and

Associates of the College, asking for ideas and suggestions for the improvement or alteration of subsequent programs. Many replies of value were received, and the answers analyzed; and an attempt has been made by your President to embody as many of the suggestions submitted as possible in the construction of the General Sessions Program. The main changes that he has attempted to make may be briefly summarized, as follows:

(1) The number of papers in the General Sessions will be fewer than has hitherto been the case—probably never in excess of eight papers, of a maximum of twenty minutes each, in any of the morning sessions, which will run from 9 until 12:30.

(2) The morning sessions will be broken mid-way by an intermission of thirty minutes, which will provide not merely a period of relaxation for the audience but will afford an opportunity for every member of the College to make a careful inspection of all of the exhibits. The importance of this cannot be over-emphasized, for it should be pointed out that the exhibits go a long way toward defraying the expenses of the Annual Clinical Session itself; and, moreover, the exhibits offered are invariably worthwhile, from the standpoint of the internist. It has been none too easy a task to assemble as many exhibits as Mr. Loveland has been successful in securing, partly for the reason that exhibitors are aware of the fact that the members of the College will probably be away from the exhibition hall at least half of each day of the Session. It is, therefore, only fair to urge that interest in the exhibits be intensely manifested at all possible times, but particularly during these intermissions which have been provided for just this purpose.

It will perhaps be of interest to know the general method that has been employed in attempting to provide interesting General Sessions. In the first place, the programs of the preceding three meetings were all carefully analyzed, in terms of subjects covered and of individual presenting essays. This analysis revealed several important and interesting facts: particularly, that in the last two years certain subjects had been, if

anything, over-handled—as, for instance, articles on tuberculosis and hypertension; and, second, the fact that the same individual had presented papers on two and sometimes on three succeeding programs. It was thought wise, therefore, to endeavor to provide a series of articles which dealt as much as possible with new subjects; and furthermore, it was decided that an individual who had appeared twice within the last preceding three years would not be invited to present a paper at this particular Session. This plan seemed manifestly fair to all to whom the problem was presented.

In the attempt to secure the greatest possible number of submitted titles, the following general method has been employed:

(1) Personal letters have been sent to a great many individuals, whether members of the College or not, throughout the entire United States and Canada.

(2) A letter was sent to the Governor of every state and territory, asking that he in turn submit the names of all Fellows, or of individuals not members of the College, in his State, who, in his opinion, might have material interesting and worthy of presentation before the College; and to every such person a letter was subsequently sent, requesting that the individual in question submit a title or titles of papers which he might care to present. It was clearly pointed out at the time that all of these letters were sent, that the mere submission of a title or titles in no way obligated the Program Committee to accept them.

The result of this extensive correspondence with men all over the country has been the submission of a great many papers, doubtless of both worth and practical interest. At this writing only a few have been finally accepted, and the final selection will be deferred as late as possible, in order that the Program Committee will have the greatest possible amount of material to select from, in its endeavor to secure new subjects, new authors and wide geographical representation. The total number of papers that can be accepted will be between forty-five and fifty, at the most; and it must be apparent that the responsibility for the final selection is no easy one, nor will final selection

be the result of personal ideas and opinions, by any means. The hope is expressed that those who have shown their willingness to read papers will clearly understand, and entertain no hard feelings, if it is found wise to reject their proposed addresses.

The number of possible symposia of great interest is very large. Under consideration at the present time are symposia on blood diseases, oxygen therapy, diseases of the liver, recent advances in endocrinology with particular reference to the newer work on supra-renal extracts, myocarditis, and several others which it is not necessary to mention. The greatest difficulty is to know which of the many equally valuable and interesting ones to accept; obviously, the individual tastes of everyone cannot be met.

#### CLINICAL SESSIONS

To Doctor Maurice C. Pincoffs, Professor of Medicine at the University of Maryland, was delegated the task of arranging for all of the Clinical Sessions. Baltimore has but two medical institutions of learning; namely, Johns Hopkins and the University of Maryland itself. Scattered throughout the city are many modern and excellently run hospitals, in which, however, little if any active teaching is done, at least in conjunction with either of the two Medical Schools. Obviously, the focus of greatest attraction will be the various departments at the Johns Hopkins Hospital and Medical School; and it should be stated at this time that the Heads of all of the Departments of this institution have expressed and are showing an enthusiastic interest in the construction of a program which will open all of the facilities of this enormous plant to the visiting members of the College. The active organization and work, in so far as it concerns the Johns Hopkins Hospital, is under the able administration of Doctor Alan M. Chesney, Dean of the Medical School, and a committee appointed by him. A similar committee, acting under Doctor Pincoffs, will supervise the Clinical Programs to be held at the University of Maryland and its affiliated Hospital. In addition, clinics, ward walks, laboratory demonstrations and the like will be held in many of the non-teach-

ing hospitals of the city, such as the Union Memorial Hospital, Saint Agnes Hospital, at which Doctor Joseph C. Bloodgood does so much of his work, the Municipal Hospitals, and several of the more private institutions, such as the Howard A. Kelly Hospital, noted particularly for its radium activities, and the Sheppard and Enoch Pratt Hospital, which is one of the most modern dealing with psychiatric problems. This does not by any means exhaust the list.

It has been customary in former meetings to have a certain number of clinics given by distinguished out-of-town clinicians, either Fellows of the College or invited guests; and this custom will be followed again this year, in all likelihood.

It should be further noted that the program, in so far as it concerns Johns Hopkins, will include both the pre-clinical as well as the clinical facilities: the work of the Harriet Lane Home in Pediatrics; the Wilmer Institute for Diseases of the Eye; the Phipps Psychiatric Institute, headed by Doctor Adolf Meyer; and, moreover, the surgical facilities of the Hospital are already being marshalled for the presentation of such border-line problems as are of equal interest to surgeons and internists alike. The Johns Hopkins School of Hygiene and Public Health, with Doctor William H. Howell as its Director, will provide its own program of subjects and demonstrations of interest particularly to Public Health workers and those deeply interested in all lines of Preventive Medicine. Last, but by no means least, the new William H. Welch Department of Medical History will offer a program unique in the annals of the College. As above stated, final details as to topics, clinicians giving them, etc., have not yet been worked out in any of the hospitals; but from the above it can readily enough be seen that plenty can and will be provided to suit the tastes and interests of everyone.

#### CONVOCATION

The Annual Convocation of the College, for the induction of new members, as Masters or Fellows, will be held on Wednesday evening, March 25, at a time and place subsequently to be announced. It is felt that

this is, or at least should be, the most formal gathering which the College holds during its Clinical Session; and it is, therefore, earnestly urged that all members and those to be inducted will appear in evening dress on this occasion, at which time the annual Presidential Address is to be given. Following the Convocation, it is hoped that an appropriate reception to the new members can be held, affording them a chance to meet and know not only the Officers of the College, but also to mingle with those who have been members for varying periods of time. Just how this can best be worked out is still under consideration, but again, it is hoped that this meeting will be fully attended.

#### ANNUAL BANQUET

As previously stated, this will be held, in all likelihood, at the Lord Baltimore Hotel on the evening of March 26, and at it all members, their wives and guests are urged to be present. The function of such a banquet, it would seem, should be not only a pleasant evening of social intercourse, but it should also provide a message of educational importance to all assembled; and with this in mind, it is now thought that the banquet will be addressed by probably a single speaker of some national or international fame and importance, rather than having the customary after-dinner speeches made by a number of individuals.

#### BUSINESS MEETING

The last half or three-quarters of an hour on the morning of March 26 will be set aside for the holding of the Annual Business Meeting of the College, at which all Fellows and Masters are earnestly urged to be present, so that they may hear in person reports as to the administration and financial status of the College. At this meeting the Nominating Committee, appointed by the President one month after the last General Session, will hand in its nominations for officers, Regents and Governors for the ensuing year; and, finally, on this occasion the incoming President, Doctor S. Marx White, of Minneapolis, will be introduced into office. It is fitting and proper that his induction be marked by a full attendance.

#### LADIES ENTERTAINMENT COMMITTEE

It is hoped and presumed that the Baltimore Session will be graced by the presence of many of the wives of the attending members of the College. Baltimore has long been famed for its hospitality, and it is an assured fact that an interested and hospitable Ladies Entertainment Committee will see to it that all visiting ladies are interestingly occupied during their stay in Baltimore. Like many other committees, the final plans have not yet been drafted; but no doubt need be entertained as to their fitness and pleasure.

#### POST-SESSION WASHINGTON DAY

It was felt that a great many of the members, particularly those coming from some distance, would not wish to return without paying a visit to the National Capital, particularly if some of the unusual medical facilities of that city could be assembled for their interest and instruction. With this in mind, the matter was taken up with Doctor William Gerry Morgan, President of the American Medical Association and Governor of the American College of Physicians for the District; and through his influence a luncheon was recently held in Washington, at which a number of men of national importance were present, including Surgeon General Ireland, of the Army; Doctor Hugh S. Cummings, Surgeon General of the United States Public Health Service; Doctor C. M. Griffith, Medical Director of the United States Veterans Bureau; Doctor W. A. White, Superintendent of Saint Elizabeth's Hospital; a representative from the United States Naval Medical School, and others, including the President of the Medical Society of the District of Columbia. These men enthusiastically offered their heartiest coöperation in the preparation of a memorable Washington Day, and the number of interesting possibilities was so great that it seemed wise, almost, to change the entire meeting from Baltimore to Washington itself. The facilities of Saint Elizabeth's Hospital and its unusual opportunities of psychiatric study, the Library of the Surgeon General, Army Medical Center, Army Medical School, Walter Reed Hospital, the Smithsonian Museum, the Institute of Public Health, will all be available in a plan

which yet remains to be worked out; and this, in turn, will depend largely upon the number of members who express their desire and intention to attend the Washington Meeting.

Such, in schematic form, is the general lay-out for the forthcoming meeting. It is

hoped that the lack of specific details will at this time incite rather than dampen further interest in the meeting itself. At least it can be truthfully stated that Baltimore's welcome will be a wholehearted and unstinting one, and it is believed that all who come will leave repaid.

#### LIST OF BALTIMORE HOTELS

The LORD BALTIMORE HOTEL will be the headquarters hotel for Officers, Regents and Governors, and so far as facilities permit, will accommodate other members and guests of the College. Reservations that the LORD BALTIMORE HOTEL cannot fill, will be referred immediately to some other hotel conveniently located. Those who plan to attend the Baltimore Clinical Session should apply directly for reservations to the hotel of their choice.

(All Prices are for Rates per Day, European Plan)

##### LORD BALTIMORE, Baltimore and Hanover (Headquarters)

Single room with bath.....	\$3.50 to \$ 6.50
Double room with bath.....	5.50 to 10.00

##### ALTAMONT, Eutaw Place and Lanvale St.

Single room without bath.....	2.50
Single room with bath.....	3.00 to 3.50
Double room without bath.....	4.00
Double room with bath.....	5.00 to 6.00

##### ARUNDEL, Charles St. and Mt. Royal

Single room without bath.....	2.00 to 2.50
Single room with bath.....	2.50 to 3.50
Double room without bath.....	3.00 to 3.50
Double room with bath.....	5.00 to 6.00

##### BELVEDERE, Charles and Chase Sts.

Single room with bath.....	5.00 to 6.00
Double room with bath.....	7.00 to 12.00

##### EMERSON, Baltimore and Calvert Sts.

Single room without bath.....	2.50
Single room with bath.....	3.00 to ....
Double room without bath.....	4.00
Double room with bath.....	4.50 to ....

##### KERNAN, Franklin and Howard Sts.

Single room without bath.....	2.00 to 3.00
Single room with bath.....	2.50 to 3.50
Double room without bath.....	3.00 to 4.00
Double room with bath.....	4.00 to 6.00

##### Mt. ROYAL, Mt. Royal Ave. and Calvert

Single room without bath.....	2.00 to 2.50
Single room with bath.....	3.00 to 3.50
Double room without bath.....	4.00 to 4.50
Double room with bath.....	5.00 to 6.00

##### NEW HOWARD, Howard St. and Baltimore

Single room without bath.....	2.50 to 3.00
Single room with bath.....	3.00 to 3.50
Double room without bath.....	4.00 to 5.00
Double room with bath.....	5.00 to 6.00



## RENNERT, Saratoga and Liberty Sts.

Single room without bath.....	2.50 to	3.00
Single room with bath.....	3.00 to	5.00
Double room without bath.....	4.00 to	6.00
Double room with bath.....	5.00 to	8.00

## SOUTHERN, Light and Redwood

Single room with bath.....	3.00 to	6.00
Double room with bath.....	5.00 to	8.00

## STAFFORD, Charles and Madison Sts.

Single room without bath.....	2.50 to	3.00
Single room with bath.....	4.00 to	5.00
Double room without bath.....	4.00 to	5.00
Double room with bath.....	6.00 to	8.00

Doctor Anthony Bassler (Fellow), New York City, is the author of a new text book entitled "Intestinal Toxemia, Biologically Considered." His text book "Diseases of the Stomach and Upper Alimentary Tract" is now in the sixth edition, and "Diseases of the Intestines and Lower Alimentary Tract" in the third.

Dr. A. S. Burdick, who has been, officially, Editor-in-Chief of *Clinical Medicine and Surgery* for a long time, has given up that title, and the Managing Editor, Dr. George B. Lake, who has conducted that journal for the past six years, becomes, officially, its Editor, Dr. Burdick retaining the leading position on its general editorial staff.

## GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made of the receipt of the following gifts to the College Library of publications by members:

Dr. Louis H. Roddis (Fellow), Washington, D. C.:

1 Book—"EDWARD JENNER AND THE DISCOVERY OF SMALL-POX VACCINATION"

Dr. LeRoy Sante (Fellow), St. Louis, Mo.:

2 Books—"LOBAR PNEUMONIA" and "THE CHEST"

Dr. Oscar W. Bethea (Fellow), New Orleans, La.:

Reprints:

"A Case of Cardiospasm"

"Biological Therapy"

"Developing the State of Well-Being"

"A Tonsil Eversor"

"The Treatment of Pneumonia"

"Lead Markers in Roentgen Examination of Diseases of the Chest"

"The Use of Lead Markers in X-Ray Examinations of the Chest"

"Typhus Fever in Louisiana"

Dr. Burton R. Corbus (Fellow), Grand Rapids, Mich.:

Reprints:

"Beaumont: Michigan's Pioneer Physiologist"

"Medical Treatment of Peptic Ulcer"

"Human Botulism: Studies in an Outbreak of Twenty-Nine Instances" (With Merrill Wells & Fred P. Currier)

Dr. E. W. Gehring (Fellow), Portland, Maine:

Reprint:

"Syphilis and Society"

Dr. Hyman I. Goldstein (Associate), Camden, N. J.:

Reprints:

"Acromegaly and Lymphatic Leukemia"

"Sarcoma of the Heart"

"Familial (Hereditary) Epistaxis" (with Henry Z. Goldstein)

"Endocarditis and Meningitis (Pneumococcic (with Henry Z. Goldstein)

"Recent Advances in Treatment"

"Hypocalcemia, with Lowered Basal Metabolism Tendency to Bleeding (Epistaxis)"

Dr. Morris H. Kahn (Fellow), New York, N. Y.:

Dr.  
Re



## Reprints:

- "'Arbitrary Period of Disability' As a Mode of Settlement in Compensation Claims"
- "Auricular Flutter Following Direct Injury to the Chest"
- "The Influence of Venous Filling on the Heart"
- "Aneurysm of the Left Ventricle"
- "Four Cases of Multiple Myeloma"
- "A Case of Subacute Infective Endocarditis with Mycotic Aneurysm and Meningeal Symptoms"
- "Serum Treatment of Postinfluenzal Bronchopneumonia"
- "Health Supervision of Employees in Financial Organizations"
- "Principles of Conducting a Cardiac Clinic"
- "Contraceptive Advice and the Medical Profession"
- "A Municipal Birth Control Clinic"
- "Elevators for Children's Schools"
- "The Human Dying Heart" (with Israel Goldstein)
- "A New Vascular Sign of Death"
- "Quinidine in Treatment of Cardiac Decompensation" (with Sidney B. Wilensky)
- "The Position of the Arm in Blood Pressure Measurements"
- "A Method for Recording Continuous Blood Pressure"
- "Present Status of Curability of Bronchial Asthma"
- "The Classification of Asthma"
- "Cardiac Asthma"
- "Angina Pectoris"
- "Etiologic Factors in Angina Pectoris"
- "Prodromal Symptoms in Angina Pectoris"
- "Cardiovascular Lesions Following Injury to the Chest" (with Samuel Kahn)
- "The Medical Critic and Guide"—Journal

Dr. William D. Reid (Fellow), Boston,  
Reprint:

- "The Diagnosis of Cardiovascular Syphilis; Analysis of Clinical and Post-Mortem Findings"

Dr. Blanton P. Seward (Associate),  
Roanoke, Va.:

## Reprints:

- "Factors in the Prognosis of Arterial Hypertension"
- "The Rational Use of Digitalis"
- "Coronary Occlusion, with Report of a Case"
- "A Clinical Study of Visceroptosis"
- "The Necessity for a Careful Pre-operative Medical Examination of Surgical Patients and the Recognition of Postoperative Circulatory Disturbances"

Dr. Virgil E. Simpson (Fellow), Louisville, Ky.:

## Reprints:

- "Gall Bladder Disease"
- "Food Content with Relation to Density and Composition of Stone in Upper Urinary Tract" (With Owsley Grant)

Dr. Walter M. Simpson (Fellow), Dayton, Ohio:

## Reprint:

- "Undulant Fever (Brucelliasis)"

Dr. Max H. Weinberg (Associate), Pittsburgh, Pa.:

## Reprints:

- "Epidemic (Lethargic) Encephalitis"
- "Unusual Case of Cerebrospinal 'Giant-Cocci' Meningitis"
- "Spinal Cord Tumors"

Dr. Harold S. Hatch (Fellow), Indianapolis, has been appointed as a member of the Board of Trustees of the State Sanatorium at Rockville, Ind.

At the Annual Fall Conference of the Oklahoma City Clinical Society, held November 5-7, 1930, the following members of the College offered clinics or demonstrations as indicated below:

Dr. P. M. McNeill (Associate); "Bronchiectasis"

Dr. C. J. Fishman (Fellow); "Demonstration of Fundamental Neurological Signs"

Dr. Ray M. Balyeat (Fellow); "Demonstration of Cases Illustrating Five Allergic Syndromes in Children"

Dr. Lea A. Riely (Fellow); "Diabetes"  
Dr. Wann Langston (Fellow); "Arthritis"

Dr. Arthur B. Chase (Fellow); "Cardiac Complications of Arthritis"

Dr. Arthur W. White (Fellow); "Gastric Ulcer"

Dr. Sydney A. Portis (Fellow), Chicago, and Dr. I. S. Trostler (Fellow), Chicago, are authors of "The Clinical Significance of Roentgenological Findings of the Non-Malignant Colon" and "A Milliampere Minute Dose Table for Superficial Therapy," respectively, in the December Issue of RADIOLOGY.

At the third spring clinical conference of the Dallas Southern Clinical Society, to be held at Dallas, Texas, March 30 to April 3, 1931, the following Fellows of the College will contribute to the program:

Dr. Walter C. Alvarez (Fellow), Rochester, Minn. and Dr. James H. Means (Fellow), Boston, Mass.

At the Scientific Meeting of the Allegheny County Medical Society, on November 18, at Pittsburgh, Dr. Ernest W. Willetts (Fellow) gave a paper on "Agranulocytosis"; Dr. Lester Hollander (Fellow) gave a paper on "Eczema from the Allergic Standpoint"; and Dr. Max H. Weinberg (Associate) presented "A Case of Pneumococcus Type III. Meningitis with Recovery; Treated with Potassium Permanganate."

Dr. Frank A. Evans (Fellow), Pittsburgh, Pa., is the author of "Pernicious Anemia," a book published by the Williams & Wilkins Co.

Dr. Oliver T. Osborne (Fellow), New Haven, Conn., is the author of an article entitled, "The Cost of Medical Care," which appeared in the Medical Journal and Record, November 5, 1930, page 426.

Dr. Ellen C. Potter (Fellow), Director of Medicine, Department of Institutions and Agencies of New Jersey, addressed the

annual meeting of School Nurses of New Jersey on the subject of "The School Nurse and Mental Hygiene" at Atlantic City, November 11; and was guest speaker at the annual dinner of the State Conference of Social Work at Wilmington, Del., November 13, her subject being, "Experiments in Democracy in the Field of Social Welfare."

Dr. Sinclair Luton (Fellow), St. Louis, Mo., gave an address on "Diagnosis of Chronic Heart Disease (with Clinical Demonstration, Lantern Slides and Moving Pictures of Heart Valves in Action)" before the Southwest Missouri Medical Society at Springfield, Mo., November 6. Dr. Luton also gave an address entitled, "Danger Signals in Chronic Heart Disease," before the forty-eighth annual meeting of the Wabash Railway Surgical Society at St. Louis, November 10.

The name of Dr. Anthony A. Rutz (Fellow), Brooklyn, N. Y., should be omitted from the present Directory of the American College of Physicians, due to his death on May 3, 1928; although not reported to the College until October 11.

Dr. Albert S. Hyman (Fellow), Director of the Witkin Foundation for the Study and Prevention of Heart Disease, Beth David Hospital, New York City, presented a paper on October 28, 1930, upon "Coronary Occlusion Simulating the Acute Surgical Abdomen; Report of three Cases Operated Upon," before the Metropolitan Medical Society.

On November 10, 1930, he presented a paper upon "Subacute Bacterial Endocarditis," before the Beth David Hospital Clinical Society.

On November 17, 1930, he gave a demonstration upon the "Irregularities of the Fetal Heart—A Phonocardiographic Study of the Fetal Heart Sounds from the Fifth to Eighth Months of Pregnancy," before the Yorkville Medical Society.

The November 17th meeting of the Yorkville Medical Association, New York City,

was a symposium upon Diseases of the Heart. The program was as follows:

Dr. Joseph B. Wolffe (Associate), Philadelphia, spoke on "The Hormone Vasodilators in the Treatment of Vascular Diseases with Special Reference to Angina Pectoris."

Dr. Aaron E. Parsonnet (Fellow), Newark, N. J., spoke upon "Myocardosis, the Failing Heart of Middle Life."

Dr. Albert S. Hyman (Fellow), New York City, spoke on "Irregularities of the Fetal Heart; A Phonocardiographic Study of the Fetal Heart Sounds from the Fifth to Eighth Months of Pregnancy."

In the International Clinics (Philadelphia), September and December 1930 volumes, appeared a paper by Dr. H. I. Goldstein (Associate), Camden, N. J., on "Osler's Disease"; "Hypocalcemia with Hypothyroidism and Tendency to Bleeding" appeared in the Medical Journal of the Medical Society of New Jersey, and Dr. Goldstein's paper on "Recent Advances in Treatment" appeared in American Medicine (New York City), July and August, 1930, Issues.

Dr. Eugene R. Whitmore (Fellow), Washington, D. C., with Dr. Wallace M. Yater, delivered a paper on "Carcinoma of the Liver" before the Medical Society of the District of Columbia on November 25. This paper was discussed by Dr. Lester Neuman (Fellow), Washington, D. C. Dr. C. B. Conklin (Fellow), Washington, D. C., is the Secretary of the Society.

Dr. Fred C. Oldenburg (Fellow), Cleveland, was elected Chief of the Medical Department of Charity Hospital; also Director of the Medical Dispensary. Both of these appointments were sanctioned by the Faculty of the School of Medicine of Western Reserve University. Dr. Oldenburg continues as Secretary of the Staff of Charity Hospital.

Dr. John P. Sawyer (Fellow), Cleveland, was elected Chief of the Staff of Charity Hospital. The appointment was sanctioned

by the Faculty of the School of Medicine of Western Reserve University.

Dr. Arthur R. Elliott (Fellow) and Dr. George H. Coleman (Fellow), both of Chicago, are President of the Chicago Society of Internal Medicine and Secretary of the Institute of Medicine of Chicago, respectively.

Dr. E. Rodney Fiske (Fellow), New York City, Lecturer, Diseases of the Chest, New York Homeopathic Medical College and Flower Hospital, is the author of an article, "Basic Principles Underlying Homeopathic Prescribing in Cardiovascular Disease." The original paper was read before the Bureau of Homeopathy at the 86th annual convention of the American Institute of Homeopathy, Atlantic City, N. J., June 18, 1930.

Dr. Ray M. Balyeat (Fellow), Oklahoma City, Lecturer on Allergic Diseases, University of Oklahoma School of Medicine, is the author of a book, "Allergic Diseases, Their Diagnosis and Treatment."

Dr. Thomas Noxon Toomey (Fellow), St. Louis, Mo., is the author of a book on Dermatology, "The Treatment of Skin Diseases in Detail."

On November 7, 1930, Dr. Curran Pope (Associate), Louisville, delivered an address over the Radiophone of WHAS, the Courier Journal and Louisville Times. The address was delivered at the request of the Disabled Veterans of Kentucky. Dr. Pope took as his subject, "For-Get-Me-Not Day."

On Armistice Day, November 11, 1930, Dr. Curran Pope, speaking under the auspices of The National Security League of New York, delivered a Radiophone talk over the Radiophone of WLAP. The subject of Dr. Pope's address was, "Armistice Day," dealing with the patriotic activities and the meaning of the day.

Dr. Edward C. Mason (Fellow) has removed from Springfield, Mo., to become connected with the Medical Department of the University of Oklahoma, and resides in Oklahoma City.

Dr. Henry M. Moses (Fellow), Brooklyn, delivered an address on "Malignancy of the Lung" before the Brooklyn Society of Internal Medicine on November 28.

Dr. Joseph G. Terrence (Associate), Brooklyn, is President of this Society.

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Dr. F. M. Pottenger (Fellow), Monrovia, Calif., gave two addresses before the Oklahoma City Clinical Society at its Annual Fall Clinic, November 5, 6 and 7th, on "The Importance of Visceral Neurology in General Medicine" and "The Conquering of Tuberculosis"; and a clinic on "The Treatment of Tuberculosis."

Dr. Pottenger also gave an address before the Wichita Medical Society, Wichita, Kansas, on the evening of November 15, on "The Diagnosis and Clinical Course of Tuberculosis."

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Dr. Benjamin Goldberg (Fellow), Medical Director of the City of Chicago Municipal Tuberculosis Sanitarium Organization, and Associate Professor of Medicine, University of Illinois, was the speaker at a joint meeting of the Jefferson County Medical Society and the Louisville Tuberculosis Association at Louisville, Ky., on Monday, December 1, 1930. His topic was Tuberculosis Control and the General Practitioner."

Dr. Goldberg also addressed a noon luncheon meeting of the Hospital Directors' Association at Louisville on the same day. At this time he spoke on "Clinic and Sanatorium Management of Tuberculosis."

Dr. Stuart Pritchard (Fellow), who for many years has been head of the Chest Department of the Battle Creek Sanitarium, has resigned this position to become the Medical Advisor of The W. K. Kellogg Foundation, which was established several months ago for the rehabilitation of underprivileged children. Dr. Pritchard will remain as a Consultant to the Sanitarium.

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Dr. Samuel M. Feinberg (Fellow), Chicago, gave an address on "Allergy" on December 4, before a meeting of the U. S. Veterans' Bureau Hospital at Dwight, Ill., and the physicians of neighboring towns.

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Dr. James Stevens Simmons (Fellow), Major, Medical Corps, U. S. Army, who has been President of the U. S. Army Medical Department Research Board at the Bureau of Science, Manila, P. I., has been transferred to Washington, D. C., and is now in charge of the Bacteriological Department of the Army Medical School.

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Dr. Carl V. Weller (Fellow), Ann Arbor, delivered a paper on "Primary Carcinoma of the Lung" before the Rochester Academy of Medicine, December 3rd.

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The Eleventh Annual Pasteur Lecture was delivered before the Chicago Institute of Medicine, November 11th, by Dr. Aldred Scott Warthin (Master), on "Problems of Latent Syphilis."

## OBITUARY

On Sunday, November 23, 1930, John Welsh Boyce (Fellow) died in Southside Hospital, Pittsburgh, following a gall-bladder operation.

Dr. Boyce was born in Sligo, Pa., in 1871 and graduated from the University of Pittsburgh School of Medicine in 1892. During his medical career he served on the staffs of the Western Pennsylvania and Southside Hospitals, was consulting physician to the Eye and Ear Hospital, and visiting physician to the City Hospital at Mayview where he gave freely of his time and talents. During the world war he served in the medical department at Camp Jackson with the rank of Major.

For more than thirty years Dr. Boyce served officially in one office or another in the Allegheny County Medical Society, and since 1921 was Associate Editor of its official organ, the Pittsburgh Medical Bulletin.

He is survived by his widow, Mrs. Tracy Carter Boyce.

Dr. Boyce, until his health began to fail, was a regular attendant upon medical meetings, and being endowed with a keen intellect, unusual facility in expression and a forceful individuality, his discussions upon his chosen field of practice, diseases of the chest, were never lacking in interest and benefit to those who were privileged to hear them.

An interesting sidelight upon Dr. Boyce's versatility is shown by the fact that early in his medical career he became interested in some phases of legal procedure, studied law, passed the state examinations and was admitted to the Allegheny County Bar.

Since 1922 Dr. Boyce has been a Fellow of the American College of Physicians and in his death the College sustains a very real loss.

—Furnished by E. Bosworth McCready, M. D., F. A. C. P., Governor for Western Pennsylvania.

## PRESTON MANASSEH HICKEY

Dr. Preston Manasseh Hickey, Professor of Roentgenology at the University of Michigan, died at his home in Ann Arbor, October 30th, 1930, from cardio-vascular-renal disease. Dr. Hickey was born in Ypsilanti, Michigan, December 3rd, 1865. He graduated from the literary department of the University of Michigan in 1888 and from the Detroit College of Medicine in 1892. He was elected a Fellow of the American College of Physicians in 1917.

Dr. Hickey was one of the pioneers of Roentgenology. At the time of the discovery of the Roentgen ray, 1895, he was practicing the specialty of laryngology and rhinology in Detroit, and was a teacher of pathology at the Detroit College of Medicine, and pathologist to the Detroit Clinical Laboratory.

An expert amateur photographer he quickly visioned the future of the X-ray in medicine, and urged upon the directors of the Clinical Laboratory the equipment of an X-ray Department that would make the new diagnostic method available to the general profession. This was the first medical X-ray apparatus, using the Ruhmkorff coil, installed in Michigan and one of the earliest in the country. The field of usefulness of the X-ray



in diagnosis and therapeutics rapidly grew and Dr. Hickey soon was compelled to devote all his time and energy to his new specialty.

He was Professor of Roentgenology in the Detroit College of Medicine from 1909 to 1922. During this period he developed into a national authority on radiology, and was a member of all the radiological societies of the country.

He was commissioned Lieutenant Colonel in the Medical Corps of the United States Army in the World War and was in command of X-ray equipment service of the A. E. F., with headquarters at Paris.

In 1922 Dr. Hickey was appointed Professor of Roentgenology at the University of Michigan, which position he held until his death. A sound, conservative and convincing teacher, his happiest moments were spent with his students in laboratory and class room. He had a charming personality and attached to himself a host of friends in this country and abroad. who deeply regret his death.

—Furnished by Charles G. Jennings, M.D., (Master), Governor for Michigan.

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Dr. Wm. A. Jenkins died at his home, 1626 Cherokee Road, Louisville, Ky., Dec. 17th, 1930, of Lymphosarcoma. A native of Kentucky, he attended the public schools of that

state, graduated from Hanover College, Indiana, receiving his Master's Degree, and his medical degree from the University of Louisville in 1897. He located in Louisville after his graduation and continued practice in that city until his death.

He was a member of the staffs of the Baptist, St. Anthony's, Deaconess, Kosair Crippled Children and Louisville Municipal Hospitals. He was a member of the Jefferson County Medical Society, Kentucky State Medical Association, American Medical Association, Southern Medical Association and the American College of Physicians. He was a member of the Delta Tau Delta and the Phi Chi Fraternities. He was professor of medicine in the University of Louisville from 1908 to 1923, when he became professor of clinical medicine and occupied that chair to the time of his death. During the world war he joined the medical corp and continued with rank of major until after the Armistice. He was also a member of the Medical Reserve Corp with the rank of colonel.

He confined his professional activities to internal medicine and enjoyed a large consultation practice. His energy, integrity and rare intellect fitted him eminently as a professor and clinician and attained for him a high position in medical circles in the mid-west and south.